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THE HEMODYNAMICS OF THE CIRCULATION IN HYPERTENSION *

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IN the past 50 years, and especially in the last 10 years, many investigators have been studying what may be called the mechanics or the dynamics of the circulation. The physiologists have succeeded in clearing up many disputed points in their work on animals; the clinicians have solved, by purely clinical observation, many of the problems which have arisen; and the physiologists and the clinicians together have studied many of the questions involved, by experimentation on human beings. Of the mass of information thus acquired concerning the dynamics of the circulation in man, much represents isolated and seemingly unrelated facts; some of it represents correlated information concerning many factors and their interrelationships. But confusion still exists, and this confusion arises from several sources: (*a*) lack of correlation in the study of separate functions; (*b*) lack of accurate methods of measuring some of the most important of these functions; (*c*) lack of uniformity in respect to the conditions under which the observations were made; and (*d*) an apparent failure on the part of many investigators to appreciate that there may not always be any constant relationship from individual to individual, among the various functions concerned.

Within the past 10 years, relatively accurate methods of measurement of many of these functions have been developed. The velocity of blood flow, for example, can now be measured with great accuracy by several methods. The venous pressure is capable of measurement by the direct method to a degree of accuracy sufficient for our purposes. The vital capacity has been known as a very accurate index of the efficiency of the circulation for many years. The measurement of the cardiac output or blood flow is, however, still a controversial subject. Many methods have been

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developed for application to the human, most of them depending upon rebreathing for their performance. Between these individual methods there is not complete agreement in the order of the figures obtained. With all these rebreathing methods, accurate results are not possible in the presence of severe congestive failure, so that although unquestionably accurate in other conditions, their field of usefulness has been limited by this drawback. Hence, a complete understanding of the hemodynamics of the circulation in heart disease in all the various states of compensation and decompensation has not been possible because of this limitation.

With the development of the dye injection method of measuring the cardiac output, we believe we have a method which accurately measures the circulation, even in the presence of severe congestive failure. We present here a study, based on this method, of the hemodynamics of the circulation in hypertension, with data concerning the changes that occur in its various functions as congestive failure develops, even to an extreme degree, and as compensation becomes reëstablished. We shall also show the relative effects upon these functions of rest alone and of rest and digitalis.

The technic of the dye injection method and the evidence for its accuracy have been reported elsewhere.[1] Briefly the principle of the method is as follows: A dye (brilliant vital red) is injected rapidly into a vein while simultaneously samples of blood are collected from an artery (femoral) into little tubes arranged around the outside of a rotating drum. The samples are timed and the concentration of dye in each successive sample is determined colorimetrically. From the resulting curve of concentration plotted against time the cardiac output is calculated by a simple formula.

Figure 1 shows a series of curves obtained in this fashion. In this figure are shown a typical curve obtained from a normal case, one from a case of hyperthyroidism, one from a typical cardiac case severely decompensated and one from a typical cardiac case previously severely decompensated but compensated at the time the test was made.

By this method we can determine: (1) the appearance time (A.T. or P.C.T.) of the dye, which indicates the pulmonary circulation time plus the time required for the dye to get to the heart from the point of injection and from the heart to the point of sampling; (2) the cardiac output (F) in liters per minute; (3) the total blood volume (B.V.); (4) the amount of blood (V) actively circulating in the heart and lungs and the great vessels of the chest. In addition, while the experiments were being carried out, we measured routinely: (5) the vital capacity (V.C.); (6) the venous pressure (V.P.) and the blood pressure and the pulse rate. From these data we also calculated; (7) the stroke volume (S.V.); (8) the work of the heart (W); (9) the work per beat (W_B); and (10) the volume clearance index (V.C.I.). This is the term we have given to a figure which is obtained by dividing the actively circulating blood volume by the stroke volume and which indicates the number of heart beats theoretically required to clear the heart, lungs and great vessels of their contained blood.

Clinically our cases were divided as follows: (*a*) 44 cases with normal cardiovascular systems, which furnished standards for comparison; (*b*) 75 cases of hypertension subdivided in the following fashion: (1) undecompensated (14 cases) which had never shown any signs or symptoms of congestive failure; (2) decompensated, subdivided into slightly decompen-

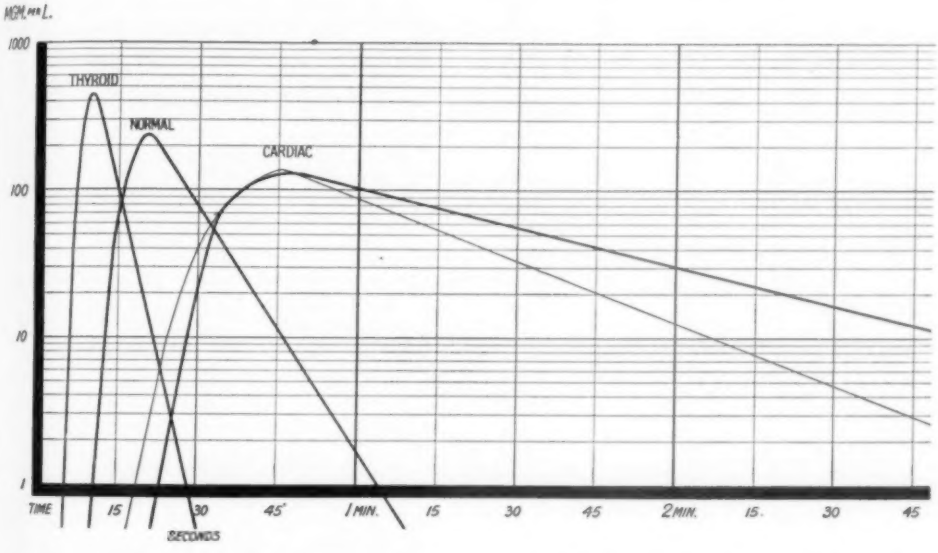

FIG. 1. Illustrating typical curves obtained in different clinical conditions. Of the two curves to the right, the one in heavier lines was obtained from a cardiac patient showing severe congestive failure, and the one in lighter lines from a patient who had been severely decompensated but who, at the time the test was made, had regained compensation.

sated (18 cases), moderately decompensated (7 cases), and severely decompensated (15 cases), depending upon the clinical impression as to the severity of congestive failure; (3) compensated (21 cases) which had previously been decompensated but which at the time of the test were perfectly compensated. Many of the cases in the latter group had previously been in the decompensated group. It should be noted that this classification was made from the clinical standpoint alone, before the results of the test were known.

Results. The results of these tests are shown in table 1 and in figures 2 and 3. Figure 2 and table 1 both demonstrate the overlapping of results, indicating that, as has been pointed out by Starr, a single individual test on any given patient may not be of much value in diagnosis due to the fact that some of the factors may fall within the normal zone.

It will be seen from a study of figure 3 that very definite and consistent changes occur as heart failure develops and progresses. In those cases which have never been decompensated the venous pressure shows a definite increase over normal, and the vital capacity is very considerably reduced. The appearance time, that is the velocity of blood flow, is not significantly

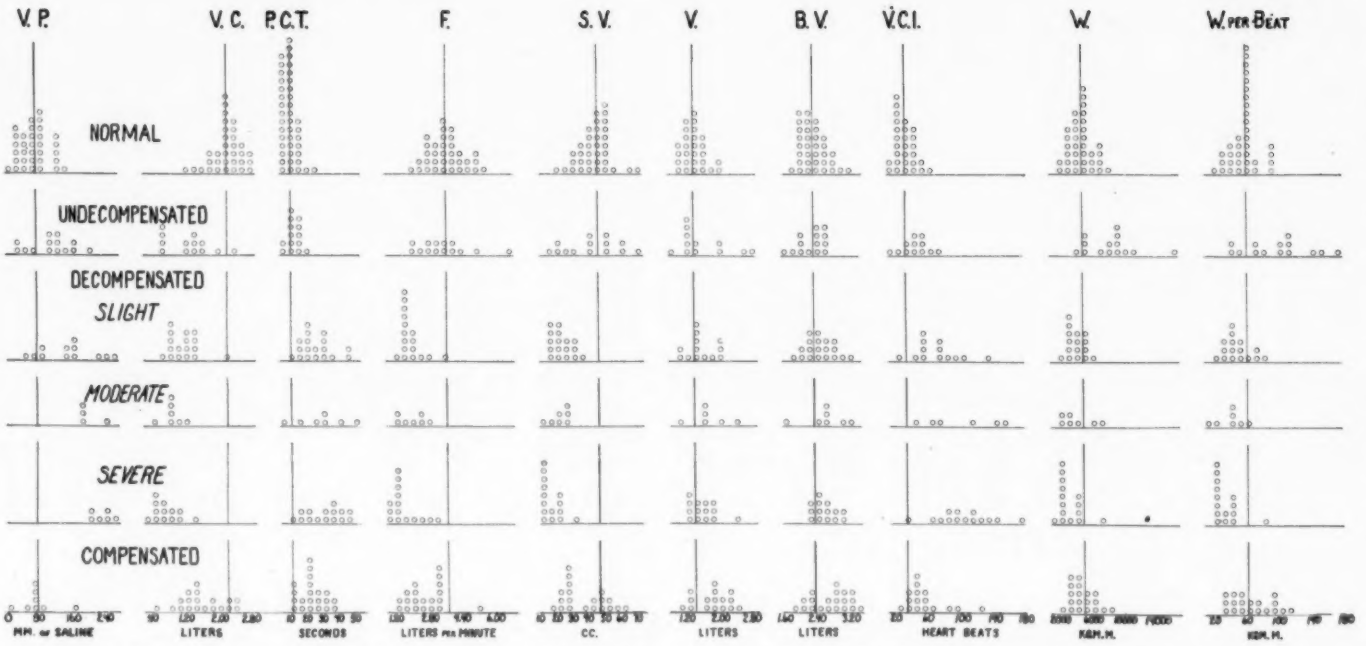

FIG. 2. Illustrating the distribution of the individual figures, showing the overlapping which prohibits any specific measurement alone in any specific case from having diagnostic significance. Each circle represents a separate measurement on a different case, the number of circles in any zone representing the number of cases. The limits of the zones are indicated by the numbers below, which refer to the appropriate units. The letters above are explained in figure 3 and in the text. The vertical lines represent the normal median value for the function.

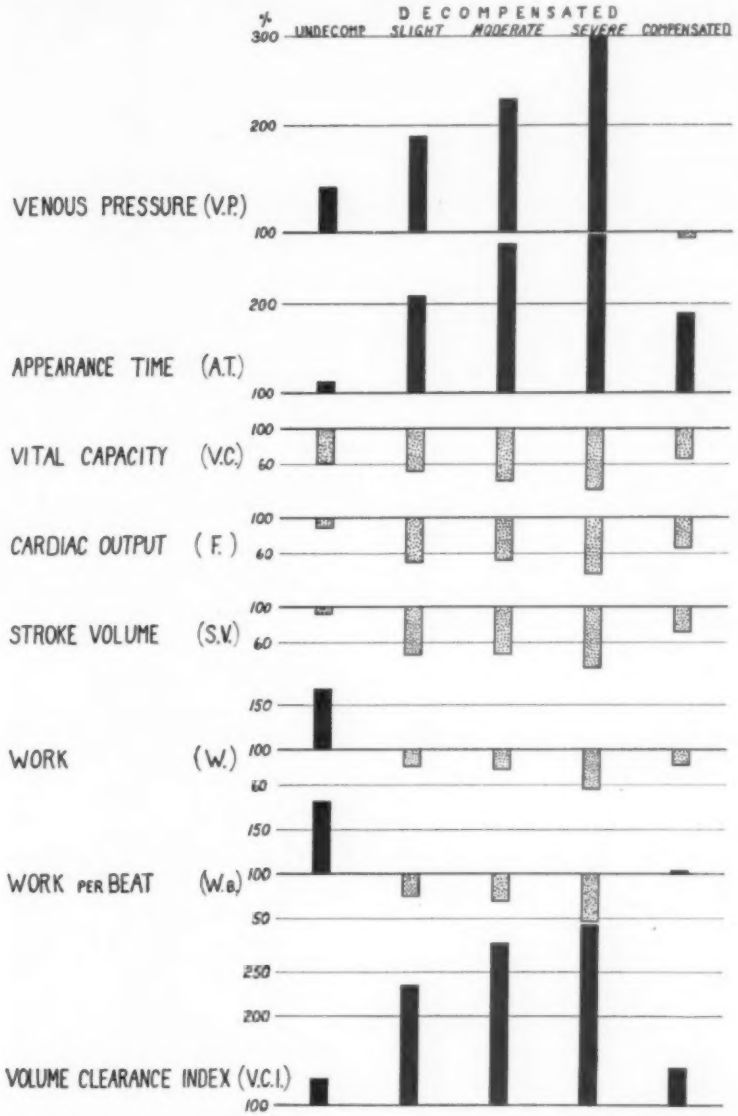

FIG. 3. Illustrating the difference in terms of percentage, from the normal. The median value of each function in each group is compared with the median value for the normal group, which is expressed as 100 per cent. The heavy solid bars represent an increase in value over the normal, and the stippled bars a decrease below the normal.

changed, however, nor is there any significant change in output and the stroke volume. The volume clearance index does not show a marked increase, though there is a moderate one. On the other hand the work of the heart shows a tremendous increase, as might be expected, since the flow is essentially normal but the blood pressure greatly increased.

When congestive failure appears, however, very definite changes occur.

TABLE I

The range of figures, the median and the percentage of the normal median, for each group. The groups were classified clinically before the results of the test were known. All figures are reduced to terms of surface area excepting the venous pressure, the appearance time and the volume clearance index; this applies also to table 2 and to the figures.

	Normal 42 cases		Undecompensated 15 cases		Decompensated						Compensated 21 cases	
					Slight 18 cases		Moderate 7 cases		Severe 15 cases			
	Extremes	Median	Extremes	Median	Extremes	Median	Extremes	Median	Extremes	Median	Extremes	Median
Venous Pressure (V. P.) (mm.)	20 150	75 (100%)	30 203	113 (151%)	56 275	156 (208%)	184 250	187 (249%)	203 261	240 (320%)	15 165	70 (93%)
Vital Capacity (V. C.) (L.)	1.35 3.01	2.31 (100%)	0.72 2.42	1.41 (61%)	0.78 2.31	1.20 (52%)	0.46 1.36	0.94 (41%)	0.37 1.54	0.71 (31%)	0.57 2.52	1.52 (66%)
Appearance Time (A. T. or P. C. T.) (Sec.)	5.7 26.0	12.0 (100%)	6.2 20.0	13.6 (113%)	13.5 48.3	25.1 (209%)	9.5 54.5	32.1 (267%)	13.5 49.0	33.3 (277%)	11.1 36.1	22.8 (190%)
Cardiac Output (F) (L/min.)	2.37 5.59	3.89 (100%)	2.01 6.88	3.46 (89%)	1.41 3.99	1.93 (50%)	1.25 2.97	2.04 (52%)	1.07 3.20	1.42 (37%)	1.49 5.48	2.57 (66%)
Stroke Volume (S. V.) (c.c.)	23.0 70.7	46.5 (100%)	18.6 74.0	43.0 (92%)	16.3 36.6	21.4 (46%)	11.2 26.0	22.0 (47%)	11.3 33.0	14.3 (31%)	19.3 60.0	33.5 (72%)
Volume of Blood in Heart and Lungs (V) (L.)	1.07 2.15	1.45 (100%)	0.99 2.85	1.36 (94%)	1.10 2.17	1.57 (108%)	1.00 2.57	1.64 (113%)	1.25 2.41	1.61 (111%)	1.09 2.45	1.94 (134%)
Total Blood Volume (B. V.) (L.)	1.89 3.25	2.40 (100%)	1.77 2.75	2.42 (101%)	1.93 3.34	2.50 (104%)	1.63 3.31	2.66 (111%)	2.20 3.04	2.59 (108%)	1.94 3.42	2.89 (120%)
Volume Clearance Index (V. C. I.) (Heart Beats)	18.9 69.7	33.0 (100%)	19.0 71.6	42.8 (130%)	29.2 133.1	77.4 (235%)	40.5 157.0	92.9 (282%)	37.8 172.0	100.1 (303%)	28.7 127.0	46.9 (142%)
Heart Work (W) (Kgm. M.)	2410 8430	5165 (100%)	5340 16280	8665 (168%)	2530 6320	4175 (81%)	2740 6950	3970 (77%)	1950 4785	2955 (57%)	2915 8285	4245 (82%)
Heart Work per Beat (W_B) (Kgm. M.)	29.0 96.2	63.0 (100%)	40.6 175.0	104.8 (182%)	28.1 83.0	47.1 (75%)	17.9 64.4	43.2 (69%)	20.5 80.7	28.7 (46%)	35.8 112.4	65.6 (104%)

The venous pressure rises and the vital capacity falls (both long known by clinical observation); the rate of blood flow slows, as shown by the increased appearance time; the cardiac output and the stroke volume both decrease to only one-half of the normal value, while at the same time the number of heart beats required to clear the heart and lungs of actively circulating blood (volume clearance index) becomes more than doubled. The work of the heart becomes reduced, not only to normal but below it, in spite of little alteration in blood pressure.

As congestive failure increases, the changes in these functions become progressively more and more marked. When decompensation has become very severe, the venous pressure has risen to more than three times the normal level and the vital capacity fallen to one-third of normal; the blood is flowing only about one-third as rapidly as before congestion appeared; the cardiac output and the stroke volume have become reduced to about one-third of the normal figure, while it now requires three times the normal number of beats to clear the heart and lungs of blood; and the heart work has been reduced to one-half of its normal value.

When compensation again becomes fully established, as a result of appropriate therapeutic measures, very interesting changes occur. As can be observed clinically, the venous pressure returns to normal, but the vital capacity does not, remaining instead at a level approximately one-third below. The rate of blood flow increases, but does not even approach the normal velocity, remaining about one-half as rapid as normal. Neither do the cardiac output and stroke volume return to normal, but remain at about two-thirds of the normal value. The number of heart beats required to clear the heart and lungs of blood also remains increased at more than 40 per cent above the normal figure. The heart work, however, again becomes normal or nearly so though it does not reach the level it did before heart failure set in.

We stated earlier in the paper that we also measured the total actively circulating blood volume and the volume of actively circulating blood in the heart and lungs and great vessels. The changes in these functions are not particularly marked, as may be seen by a study of table 1 and figure 2. It is very interesting, however, that the changes which do occur are strikingly parallel for the two. In general, it may be said that before congestive failure develops, there is no essential change in either; as congestion develops they both increase, becoming slightly greater as congestion increases. As compensation becomes reëstablished, they increase greatly and significantly (to 134 per cent and 120 per cent respectively, of the normal value).

A comparison was made in these cases between the effects of rest alone and rest plus digitalis on these various functions. The result of this appears in figure 4 and table 2. It will be noted that, although rest alone produces a change toward normal in all of the functions, yet this change is not nearly as striking as occurred after digitalis was administered. Many

Heart Work per Beat (Wb) (Kgm. M.)	29.0 96.2	63.0 (100%)	40.6 175.0	104.8 (182%)	28.1 83.0	47.1 (75%)	17.9 64.4	43.2 (69%)	20.5 80.7	28.7 (46%)	33.8 112.4	65.6 (104%)

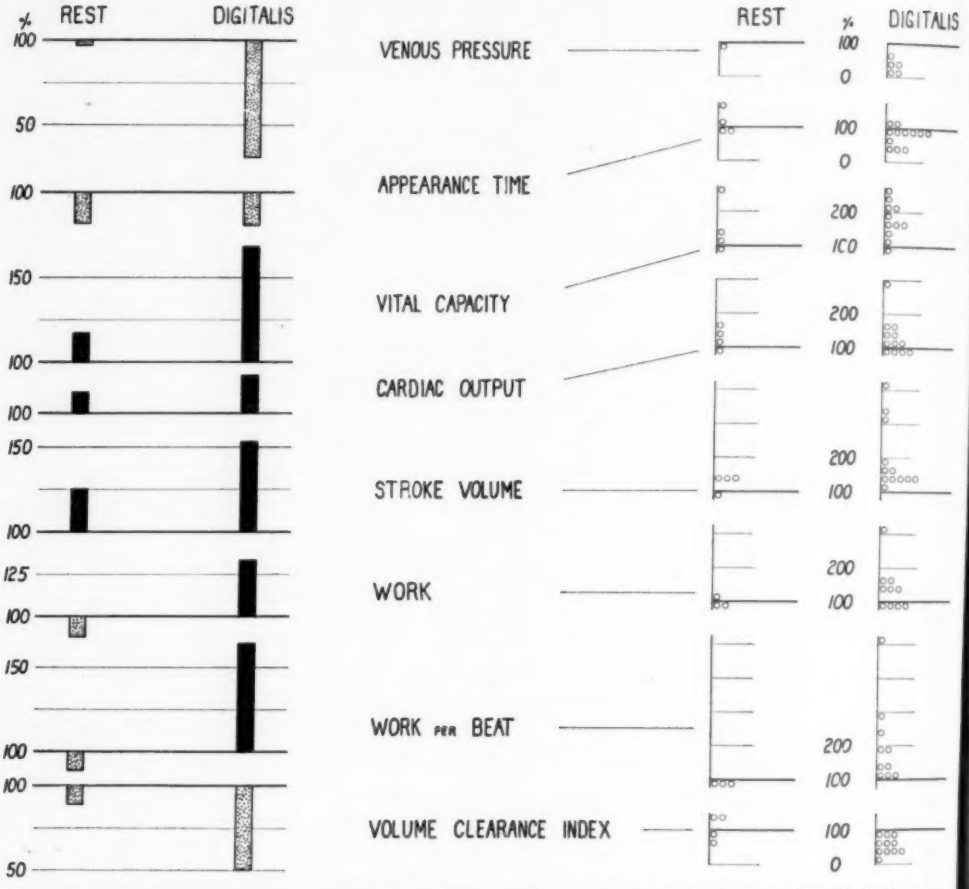

FIG. 4. Illustrating the comparative effects of rest alone and of rest plus digitalis on the various functions of the circulation in congestive failure. The horizontal heaviest lines represent the previous (decompensated) median level for the group as a whole, and is taken as 100 per cent. The height or depth of the bars represents the percentage change from that previous level. The medians are taken in all instances. The right half of the figure shows the distribution of the percentile changes from the decompensated levels, each circle representing, as in figure 2, an individual case, and the changes being divided into zones.

of these patients had bed rest for as long as two weeks between the determinations, giving the circulation ample opportunity to readjust itself without help, if it could do so. The right-hand side of figure 2 represents the distribution of the individual cases in regard to the various functions outlined.

DISCUSSION

The observations reported here, concerning many of the functions of the circulation, are not new. The progressive increase in venous pressure and decrease in vital capacity as congestive failure develops have been known clinically for many years. The slowing of the blood flow under these conditions has been assumed for a long time and was demonstrated con-

clusively by Blumgart and by ourselves as far back as 1927.[2] So, too, observations concerning the cardiac output, unreliable though they are considered by some, have been in keeping with our own. But we feel that a correlated picture of all of these functions, observed in a series of cases large enough to be considered of significance, can give us a more complete picture of what happens to the circulation as a whole, than grouping together observations on one or only a few of the many functions of the circulation. This assumes especial significance when we consider variations in individual cases. A perusal of figure 2 will illustrate this to some extent by the evidence of overlapping of results shown there. It must be remembered that we have dealt here with groups, showing the tendencies exhibited by such groups as a whole. But it must not be assumed that each individual case behaves always as the group characteristically does.

For example, in four cases picked from the severely decompensated group (see table 3), case 161 with the lowest vital capacity of all, had the quickest appearance time and the highest output; whereas case 182, with a vital capacity nearly three times as great, had the slowest appearance time and the lowest output, though the venous pressure was the same in both cases; and case 90 with the highest vital capacity of all, had an appearance time and an output intermediate in position. Thus throughout all of our observations we encounter many variations, where sometimes, for example, the flow may be normal and the velocity of blood flow decreased, or vice versa. Therefore, it is apparent that not the observation of one or two or three functions only, but the measurement of all of them simultaneously will give us the true picture of the circulatory state in any given individual.

Starr [3] has shown that in normal persons there is a linear relationship (within limits) between heart work and heart volume; that as the heart volume increases the heart work increases also; whereas in congestive failure the increase in heart volume and the decrease in heart work throw this relationship outside the normal zone. We have taken teleroentgenograms on most of our patients, and although we have not yet analyzed the results, it is apparent that the coördinates of work plotted against volume are far outside the normal zone. In this respect our results agree perfectly with those of Starr, although his method of determining heart work is based on rebreathing.

The lack of marked changes in the volume of blood in the heart, lungs and great vessels might cause one to assume that our method of measuring this factor was at fault since it is obvious from both clinical and postmortem experience that the lungs and great vessels do become engorged with blood as congestive failure develops. However, it must be borne in mind that we are measuring only the actively circulating blood, and that stagnant blood is not accounted for. Though the change is not great, there is a decided tendency for even the actively circulating blood in the heart, lungs, etc. to become increased as congestion develops; moreover, the changes in the volume

TABLE II

The effects of rest alone and of rest plus digitalis upon the various cardiac functions studied. In each group of three figures, the first represents the figure obtained when first tested, while decompensated, the second the figure at a later date, after rest or digitalis, and the third the percentile change of the second figure from the first. The figures at the foot of the columns represent the median percentile change in that group for the function in question. The state of compensation is represented as: o, fully compensated; +, ++, +++, slightly, moderately and severely decompensated respectively. The letters above are explained in table 1.

Rest

Case No.	State of Compensation	V. P. mm.	V. C. L.	A. T. Sec.	F. L/min.	S. V. c.c.	V. L.	B. V. L.	V. C. I. H. B.	W. Kgm. M.	W_B Kgm. M.
23	+++		0.71	16.5	2.83	20.0	1.66	2.20	84.6		
	+		0.86	13.5	3.99	26.6	1.55	2.48	57.9		
			+21%	−18%	+41%	+33%	−8%	+13%	−32%		
31	++		0.46	43.8	1.64	21.0	2.06	3.31	111.7	3235	41.5
	o		1.27	32.8	2.55	29.0	2.35	2.95	82.6	3225	35.8
			+76%	−25%	+56%	+38%	+14%	−11%	−16%	±0%	−14%
73	++	184	0.94	17.5	2.79	26.0	2.16	2.58	61.4	6950	64.4
	+	178	0.88	19.8	2.30	21.0	1.62	1.93	77.4	5755	58.1
		−3%	−6%	+13%	−18%	−13%	−25%	−25%	+26%	−17%	−10%
40	+		1.28	15.5	3.14	36.0	1.05	2.35	29.2	6320	71.8
	o		1.50	25.8	3.53	45.0	1.86	2.13	41.6	5185	65.6
			+17%	+66%	+12%	+25%	+77%	−9%	+42%	−18%	−9%
		−3%	+19%	+3%	+27%	+29%	+3 %	=10%	+5%	=17%	−10%

Digitalis

16	+++		0.50	41.5	1.32	14.0	1.76	2.67	128.6	2780	28.7
	+			20.3	1.63	22.0	1.10	2.00	50.3	4210	53.2
				−51%	+24%	+57%	−38%	−25%	−61%	+51%	+85%
24	+++		0.83	36.6	2.44	24.0	2.41	3.04		4480	44.8
	+		1.21	31.0	2.30	30.0				3660	48.1
			+46%	−15%	−6%	+25%				−18%	+7%
53	+++	250	0.73	24.3	1.42	13.5	1.39	2.71	101.9	2955	28.2
	+	140	1.40	25.3	1.41	16.0	1.57	2.89	97.4	2530	28.1
		−44%	+92%	+4%	−1%	+19%	+13%	+7%	−4%	−14%	±0%

TABLE II—*Continued*

Digitalis

			−44%	+92%	+4%	−1%	+19%	+13%	+7%	−4%	−14%	±0%

TABLE II—*Continued*

Digitalis

Case No.	State of Compensation	V. P. mm.	V. C. L.	A. T. Sec.	F. L/min.	S. V. c.c.	V. L.	B. V. L.	V. C. I. H. B.	W. Kgm. M.	W_B Kgm. M.
25	+ + +		1.13	33.2	1.53	13.0	1.47	3.03	111.9	2705	24.2
	o		1.85	31.8	2.32	42.0	2.36	3.35	55.4	3785	68.8
			+64%	−4%	+52%	+223%	+61%	+11%	−50%	+40%	+184%
47	+ + +		0.53	18.0	1.55	14.3	1.34	2.44	94.4	2970	27.5
	o		1.11	16.2	2.06	27.0	1.09	2.15	40.4	2915	39.4
			+109%	−10%	+33%	+89%	−19%	−12%	−57%	−2%	+43%
83	+ + +	210	0.92	47.7	1.07	11.3	1.94	2.50	172.0	1950	20.5
	o	70	1.98	14.7	3.23	46.8	1.34	3.04	28.7	6415	93.0
		−67%	+115%	−69%	+201%	+314%	−31%	+22%	−83%	+220%	+420%
135	+ + +	230	0.54	35.9	1.35	16.8	1.88	2.34	112.	2440	30.5
	o	15	1.23	28.8	2.11	25.1	2.35	2.31	93.	3300	39.3
		−93%	+128%	−20%	+56%	+49%	+45%	−1%	−17%	+35%	+29%
18	+ +		1.18	32.1	2.04	22.0	1.62	2.66	74.1	3970	43.2
	+		1.12	25.7	1.99	32.0	1.46	2.36	45.4	5145	83.0
			−5%	−20%	−2%	+45%	−10%	−11%	−39%	+30%	+92%
82	+ +	184	0.94	32.2	1.25	11.2	1.65	2.77	148.0	2005	17.9
	o	57	2.52	36.1	1.49	38.3	2.45	2.95	63.5	3305	42.9
		−69%	+168%	+12%	+19%	+245%	+49%	+7%	−57%	+65%	+140%
23	+		0.86	13.5	3.99	26.6	1.55	2.46	57.9		
	o		1.29	11.1	5.48	45.0	1.62	3.11	34.4		
			+50%	−18%	+37%	+69%	+4%	+26%	−41%		
50	+	275	1.37	46.1	2.24	19.0		2.69		4570	38.1
	o	64	2.30	21.9	1.99	23.0		2.16		4090	47.0
		−77%	+68%	−52%	−11%	+41%		−20%		−10%	+23%
138	+		0.80	48.0	1.93	21.4		2.45			
	o		0.99	34.7	2.07	28.8		3.16			
			+24%	−28%	+7%	+35%		+29%			
		−69%	+68%	−19%	+22%	+53%	+4%	+7%	−50%	+33%	+64%

TABLE III

Data of four cases chosen from the 15 cases in the severe congestive failure group, to illustrate the wide variation in individual functions of the circulation and to emphasize that one must take into consideration all of the functions and not one or two individual ones in order to determine the true state of the circulation.

Case No.	V. P.	V. C.	A. T.	F.	S. V.
161	203	0.37	13.5	3.20	33.0
84		0.50	41.5	1.32	14.0
182	210	0.92	47.7	1.07	11.3
90		1.54	27.0	1.88	20.0

of blood in the heart, lungs and great vessels are greater than the changes in total blood volume, indicating in this fact alone, a tendency for the blood to accumulate in the thorax and abdomen. The increase after compensation becomes reëstablished indicates that there must be liberated into the blood stream considerable quantities of blood previously stagnant and out of circulation. It follows also that the term " volume clearance index " indicates the number of heart beats required to clear the heart and lungs of *actively circulating* blood.

One other feature should be emphasized: It is an important fact that when compensation becomes reëstablished after congestive failure has once developed, certain of the functions of the circulation do not return to normal, notably the velocity of blood flow and the cardiac output. It may be stated in another fashion, that once heart failure has developed, the heart may never be the same again.

SUMMARY

1. Using the dye injection method, the various functions of the circulation were studied in cases of hypertension before congestive failure had developed, when congestion had appeared and when compensation had become reëstablished.

2. The changes in venous pressure, vital capacity, appearance time (velocity of blood flow), cardiac output, stroke volume, volume of actively circulating blood in the heart, lungs and great vessels, total blood volume, volume clearance index (the number of heart beats required to clear the heart, lungs and great vessels of actively circulating blood), work and work per beat are reported and discussed.

3. The relative effects of rest alone and of rest plus digitalis are reported.

4. Emphasis is laid upon the fact that even in severe heart failure certain of the functions, as the flow, for example, may be within normal limits, and that only by a study of the interrelationships of all of the functions concerned can a true picture of the cardiac hemodynamics be obtained.

BIBLIOGRAPHY

1. HAMILTON, W. F., MOORE, J. W., KINSMAN, J. M., and SPURLING, R. G.: Simultaneous determination of pulmonary and systemic circulation times in man, and of a figure related to cardiac output, Am. Jr. Physiol., 1928, lxxxiv, 338–344.

KINSMAN, J. M., MOORE, J. W., and HAMILTON, W. F.: Studies on circulation. I. Injection method; physical and mathematical considerations, Am. Jr. Physiol., 1929, lxxxix, 322–330.

MOORE, J. W., KINSMAN, J. M., HAMILTON, W. F., and SPURLING, R. G.: Studies on circulation. II. Cardiac output determinations; comparison of injection method with direct Fick procedure, Am. Jr. Physiol., 1929, lxxxix, 331–339.

MOORE, J. W., HAMILTON, W. F., KINSMAN, J. M., and SPURLING, R. G.: Studies on circulation. III. Description of injection method of studying circulation, with some clinical applications, Southern Med. Jr., 1930, xxiii, 1131–1135.

HAMILTON, W. F., MOORE, J. W., KINSMAN, J. M., and SPURLING, R. G.: Studies on circulation. IV. Further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions, Am. Jr. Physiol., 1932, xcix, 534–551.

2. BLUMGART, H. L., WEISS, S., and YENS, O. C.: Studies on velocity of blood flow, Jr. Clin. Invest., 1927 iv, 1–13, 15–31.

3. STARR, I., JR., and OTHERS: Studies of heart and circulation in disease; estimations of basal cardiac output, metabolism, heart size and blood pressure in 235 subjects, Jr. Clin. Invest., 1934, xiii, 561–592.

VASCULAR DISEASE IN THE OBESE DIABETIC, AND IN NON-DIABETICS; A DISCUSSION OF ARTERIOSCLEROSIS AS A CAUSE OF DIABETES *

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Most older diabetic patients are obese or have been so. Their pathological state is, therefore, essentially that of obesity with superimposed diabetes. The association of vascular disease and diabetes in this group is far too frequent to be ascribed to coincidence alone. Those [1, 2, 3, 4] who believe that diabetes hastens the approach and accelerates the development of arteriosclerosis refer to atheromatous lesions of the elastic and muscular arteries. The demonstration of calcium roentgenologically in the peripheral vessels has been used to detect this type of lesion, though it is realized that extensive atheromatosis may be present with minimal or even with no calcification. Such deposits occur in the deeper layers of the intima and in the media. There is some question whether sclerosis of the Mönckeberg type is related to or may be part of atherosclerosis,[5] as originally thought by Marchand. There is no essential difference, pathologically, between the sclerosis that occurs in the older diabetic and senile atherosclerosis. In analyzing the pathological descriptions of the arteries of legs amputated for gangrene at the Buffalo General Hospital, it was found that they were similar in both the diabetic and senile types. The senile group, however, was about 10 years older than the diabetic. There was close correspondence between calcium demonstrated roentgenologically and histologically. Such calcification is found more regularly in men, both diabetic and non-diabetic. Its presence increases the probability of occlusion, as has been shown by Lansbury and Brown,[6] although extensive calcification may be present for a long period with open arteries.

It is assumed that those who have suggested that diabetes in older people may be caused by arteriosclerosis of the pancreatic vessels, which in turn produce hyalinization and fibrosis of the islands, refer mostly to arteriolar lesions. These are not necessarily associated with calcification and lipoid deposits in the larger vessels, but are more intimately related to high blood pressure. These two types of sclerosis may be and commonly are found together, particularly in older people with hypertension.

The histological demonstration in diabetic patients of sclerosis of the small pancreatic arteries and arterioles, or even atherosclerosis of the larger ones, does not permit one to assume that these lesions were present at the

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time the patient developed diabetes, which usually is many years before death. In fact, it is often impossible to estimate the time of onset of diabetes in an elderly patient. If it could be shown that vascular disease was more frequent in the early diabetic than in the non-diabetic, this would constitute additional evidence that the pancreatic vessels had a greater chance of being involved. In this study only obese subjects were used because of the predominance of obesity in the older diabetic; and also so that the factor

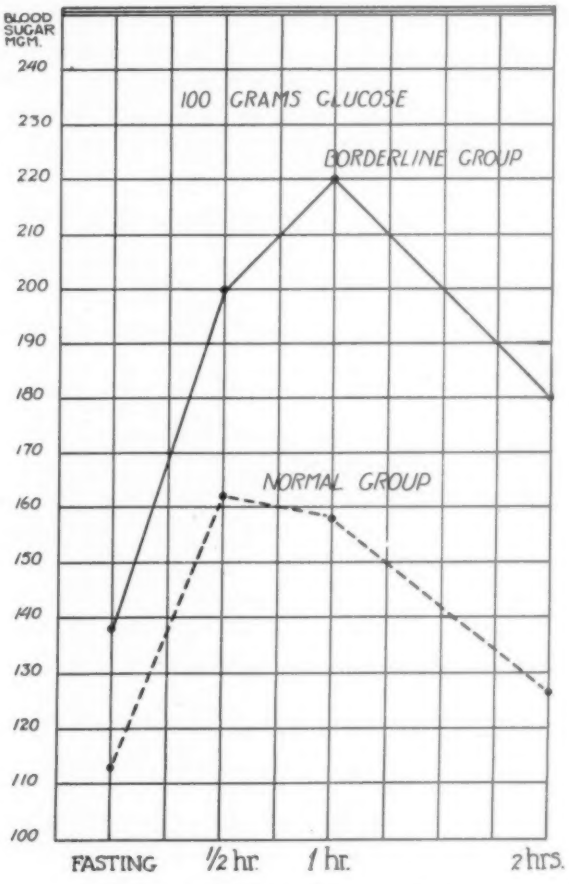

CHART I. Composite Tolerance Curves.

of body weight, which is so important in vascular disease in older people, should be adequately controlled. Previous studies, we believe, have not taken this factor sufficiently into account.

The patients were observed almost entirely in the Out-Patient Department. They were generally without symptoms, except those attributable to obesity. None of the diabetics required insulin. Calcification of the arteries of the lower extremities was searched for roentgenologically, their

blood pressures were followed, and their retinal arteries were studied by the ophthalmologist (J.G.F.). The heart was not considered, because previous workers [7, 8] have shown that obese patients as a rule have large hearts and that frequently changes in the electrocardiogram are present. The patients were divided into three groups according to their glucose tolerance. The test used was 100 grams of glucose administered by mouth, subsequent to the taking of a fasting blood sugar, and absorptive blood sugar determinations taken at one-half hour, one hour, and two hour intervals.* In the diabetics this was not done because the diagnosis was evident. There were 49 patients, with an average age of 39 years, in the group with normal glucose tolerance. Three of these were men. Seventeen women, with an average age of 43 years, comprised the group with borderline reactions to glucose. Thirty patients, five of whom were men, made up the diabetic group. We were reasonably certain that none of this group had been diabetic for over three years. Most of them had been under active treatment.

Extreme calcification of the leg arteries was found in only two patients, both men, a diabetic 67 years old and a non-diabetic 75 years old. Traces of calcification in only the dorsalis pedis arteries occurred in two of the diabetic women. The other patients in all groups had no discernible arterial shadows.

Patients were regarded as having hypertension if the blood pressure exceeded 150 mm. of mercury systolic or 100 mm. diastolic, or both. According to this definition it was present in 50 per cent of the diabetic group, 43 per cent of the borderline group, and 31 per cent of those with normal glucose tolerance. These were further separated into those who had well established hypertension and those whose blood pressure was only slightly above the borderline, for the reason that a slightly elevated blood pressure is common in obese people and that it so frequently drops with the reduction of body weight. The incidence of well established hypertension occurred about equally in the normal and diabetic groups, the incidence being 18 and 20 per cent respectively. The borderline group, a much smaller one, showed an incidence of 31 per cent. The average age of those who had such hypertension was the same in each group, 49 years.

The following criteria for the presence of retinal arteriosclerosis were used: contraction of the lumen, venous compression at the arteriovenous crossings, translucency and visibility of arterial wall, the light reflex stripe of the arteries, tortuosity of arteries and capillaries, and sclerosis of choroidal blood vessels (tesselated fundi and colloid excrescences).[9, 10, 11, 12]

A fundus was pronounced completely negative if none of these signs were present; suggestive ($\pm$), when tortuosity, reduced translucency, and disturbances of the reflex stripe occurred together; definite ($1+$), when thinning of the arteries, uneven caliber and compression of the veins oc-

* Blood sugar method: Meyer-Benedict technic.

curred singly, or together, or in combination with the above mentioned signs. When these changes were more extreme, a 2+ designation was used, and when they were observed in combination with retinal degenerative changes, such as hemorrhages or exudates, the symbol 3+ was employed.

Retinal arteriosclerosis of all grades was found in 36.6 per cent of the diabetic group, 41 per cent of the borderline group, and in 32.6 per cent of those having normal glucose tolerance. The average age of the patients having retinal arteriosclerosis was 53, 50.5, and 50.6 years, respectively. The percentage of patients with hypertension, who also had evidence of retinal arteriosclerosis, was about the same in the diabetic and borderline groups, 72.7 and 71 per cent, while that in the normal group fell to 44 per cent. This is possibly because the patients in the normal group who had hypertension were younger than those in the other groups. The average

TABLE I

Summary of Data

	Diabetic	Borderline	Normal
Number of Cases	30	17	49
Average Age	50	43	39
Percentage Weight Above Ideal	45.8	65	66
Percentage with Hypertension	50	43	30.6
Average Age with Hypertension	53	51.6	46
Percentage with Well Established Hypertension	20	31	18
Average Age with Well Established Hypertension	49.6	49	49
Percentage with Retinal Arteriosclerosis (All Grades)	36.6	41	32.6
Average Age with Retinal Arteriosclerosis	53	50.5	50.6
Percentage of Hypertension with Retinal Arteriosclerosis	72.7	71	44
Average Age with Hypertension and Retinal Arteriosclerosis	55.6	51.6	49

TABLE II

Grades of Retinal Arteriosclerosis

Group	Average Age	±	+	++	+++	Percentage (+ or more)
Diabetic (30 cases)	50	4	2	2	1	17
Borderline glucose tolerance (17 cases)	43	2	3	2		30
Normal glucose tolerance (49 cases)	39	2	9	4	1	28.6

ages of patients with both hypertension and retinal arteriosclerosis were 55.6, 51.6, and 49 years, respectively. The percentage of patients in all groups who had 2 + or 3 + retinal arteriosclerosis was the same, 10 per cent; hypertension was present in all but one of these cases. Only two patients had a 3 + retinal arteriosclerosis: one, a diabetic 60 years old, hypertension, and the other a 54 year old woman with mild hypertension and normal glucose tolerance.

With the tests used, slightly less than half of our obese subjects, diabetic and non-diabetic, had no evidence of vascular disease. Were it possible to calculate the influence of the age difference which exists in the three groups, it seems probable that the incidence of vascular disease would be about the same in each group. Also, in obese subjects there appears to be no striking correlation between glucose tolerance, hypertension, or retinal arteriosclerosis.

Discussion

Vascular disease is common in obese people, and it is a frequent cause of death in such subjects. Hartman and Ghrist [13] analyzed the blood pressures of 2042 consecutive patients, males and females about equally divided. They found the blood pressures of the overweight group to be about 12 per cent higher than those in the underweight. Dublin [14] has shown by a medical-actuarial investigation that the death rate from arterial disease was decidedly increased in individuals who were overweight, especially after 45 years. At that age the death rate for those of normal weight was 45 per 100,000, but for those whose weight was 15 to 24 per cent increased, the death rate was 97. Preble [15] in his study of 1000 patients with obesity found the average blood pressure of those after the age of 40 to be 160 systolic and 100 diastolic. Fifty-three of 700 of these patients had glycosuria, the greater number of them being in the fifth decade. Master and Oppenheimer [7] found hypertension (blood pressure 150 mm. systolic, or more) in 67 per cent of 97 patients with obesity. Their ages varied from 10 to 58 years, but nearly all of them were between 35 and 50. Smith and Willius [8] made a post-mortem study of 136 obese patients, who were more than 13 per cent overweight and whose average age was 52.1 years. Only four had diabetes. We judge that many of the deaths were postoperative. Forty-five per cent had had "well marked hypertension." Of these the average blood pressure had been 175 systolic and 82 diastolic. These figures attest the high incidence of vascular disturbances in obesity. If it could be shown that obese diabetics had a higher blood pressure than obese non-diabetics, then hypertension might be held a contributory factor to diabetes in such cases. Also, if hypertension with arteriosclerosis in itself were a cause of diabetes, then it would be expected that more patients with hypertension, even those without obesity, would develop clinical diabetes. A survey of several textbooks and clinical studies of large series of cases of hypertension did not give any information on this point. Certainly it is not our clinical impression that diabetes is an important sequel of hypertension. It is well known that extreme arteriolar sclerosis of the pancreatic vessels is common in patients with so-called malignant hypertension or sclerosis; yet, clinical diabetes in such patients appears to be uncommon.

Patients with hypertension frequently have slight glycosuria, high renal thresholds for sugar, and a distortion of the so-called normal curve after the ingestion of glucose. Different observers vary widely in their findings

and opinions on this point, as John [16] has brought to our attention. He found in a study of the glucose tolerance of 50 of his own patients with hypertension that the number of "diabetic curves" increased with age. This would suggest that hypertension produced an increasing insufficiency of insulin. Rømcké,[17] however, made similar observations, but also showed that the absorptive blood sugar curve was much the same in older people whose blood pressures were normal. Marshall [18] likewise found distinct and prolonged hyperglycemia in 50 per cent of healthy old people after the ingestion of glucose. Many terms have been given to such distorted curves. "Potential diabetes" or "pre-diabetes" are common. Schmidt [19] proposed "sthenischen Diabetes" and Kylin [19] "hypertonie Diabetes." There is insufficient proof that patients who have abnormal curves develop clinical diabetes with enough regularity to justify the word "diabetes" in the nomenclature. The various factors, which affect the inflow and outflow of glucose in the blood stream, are involved and complicated. We believe that such a test cannot safely be considered specific for clinical diabetes unless fasting hyperglycemia is present and then only under certain conditions. The patient should previously have been eating an unrestricted diet. Also, there should be freedom from hyperthyroidism, fever, and nitrogen retention.

In 1894 Hoppe-Seyler [20] reported the autopsy findings in a case of diabetes in which he believed the islet changes were caused by arteriosclerosis. In 1904 he [21] added nine such cases. Upon examination of his material, it was found that all of his patients had generalized arteriosclerosis and that the majority were in the seventh decade; three had gangrene of a lower extremity. He also examined the pancreatic vessels of a larger group of non-diabetics of the same age. He found that the diabetics had a higher grade of sclerosis of the pancreatic vessels and that in them pancreatic cirrhosis was more extensive. It was his idea that the changes in the islands were entirely secondary to the vascular changes.

Similarly, Herxheimer [22] contends that arteriosclerosis is a prominent primary factor in the production of diabetes in older people. He has drawn the analogy between nephrocirrhosis produced by arteriosclerosis and pancreatic cirrhosis.

Pathologists generally agree that sclerosis of the pancreatic vessels is a common finding in older patients. Barron [23] concludes that pancreatic atherosclerosis is frequently encountered and that it is a probable cause of diabetes. Cecil [24] found that most middle aged patients had some degree of such sclerosis and expressed the opinion that hyalinization and fibrosis of the islands were produced in a manner similar to such changes in the glomeruli.

Kraus [25] after a study of the structural changes in all of the endocrine glands in diabetics concluded that all diabetes was pancreatogenic; but he believed that there was, in spite of the great variability of the findings, a

contrast between the pancreas of the young and older diabetic. The pancreas was smaller in the young; atrophy or hydropic degeneration of the islands—the elective island disease of Weichselbaum—was commonly seen. In the older patient the pancreas showed inter- and intra-acinous connective tissue proliferation, cirrhosis, lipomatosis, and atrophy of the tubules. The changes in the islands were predominantly hyaline. A majority of the older patients showed sclerosis of the pancreatic arteries. He encountered some pancreases of older patients in which the changes commonly found in youthful patients were present, and vice versa.

Warren [26] studied 259 pancreases of diabetic patients. He thought the islands normal, as far as could be determined histologically, in 27 per cent. No definite correlation between island lesions and intra-acinar fibrosis could be determined. Fifteen of the 259 showed marked sclerosis of the pancreatic vessels. He comments that the splenic artery, which is on the same circuit as the pancreatico-duodenal artery, often shows extreme sclerosis, while the arteries of the pancreas may be relatively free. He believes that from a pathological viewpoint arteriosclerosis is not an outstanding cause of changes in the islands.

Peterson [27] considered the subject of diabetes and arteriosclerosis pathologically. He found some degree of sclerosis of the arteries and arterioles of the pancreas in nearly every case. He states, "It appears that disease of the arteries and arterioles is much more advanced in diabetics than in non-diabetics of the same age. It may be inferred that diabetes hastens the development of the arterial disease. It may be contended that arterial changes come first and cause diabetes; but the degree of involvement in many instances seems hardly sufficient to cause such a damage to the pancreas; and, also, sclerosis of the pancreatic vessels is not always associated with diabetes. I am inclined, therefore, to adopt the view that diabetes hastens the development of arteriosclerosis in some way."

It appears then that some authors, when speaking of sclerosis of the pancreatic arteries, refer to the larger vessels, while others refer to the smaller. The recent work of Rosenthal [28] leads one to suspect that atherosclerosis and arteriolar sclerosis are, possibly, in some way related. He considered this subject critically from clinical and postmortem material and concludes that hypertension plays an important rôle in the development of atherosclerosis, but he believes that there are etiological factors other than hypertension, since 48 per cent of his cases of atherosclerosis did not have hypertension. Pathologists agree that atherosclerosis of the larger arteries is not a common finding in early hypertension.

All three clinical states under consideration, obesity, hypertension, and diabetes, appear to be unquestionably influenced by an hereditary factor. All three may be found together, or in various combinations. It appears clear that obesity increases the likelihood of both diabetes and hypertension, but less certain that the presence of hypertension contributes to the proba-

bility of diabetes, since the incidence of hypertension is about the same in the non-diabetic obese person as in the obese diabetic.

With the mechanism of the production of diabetes so incompletely understood, its pathologic anatomy so variable, and, also, the possibility of extra-pancreatic influences so definite, it is not surprising that many should regard the inception of diabetes as a functional disturbance. One finds it difficult to believe the cause as being one thing in youth and as belonging to the degenerative diseases after the age of 40, as Enklewitz [29] has recently propounded. Perhaps it is more logical to think of it as a different reaction at various ages. It is conceivable, also, that the presence of vascular degenerative changes in the pancreas may be a factor in the production of diabetes, but it seems unlikely that it is the sole cause. If it were so, diabetes in the aged and in patients with high grade hypertension should be more common, unless an elective vascular disease of the pancreas exists. Also, atherosclerosis in older people is more common in men than in women. Diabetes, however, in the same age group is more common in women.

Summary

Calcification of the arteries of the lower extremities (demonstrated roentgenologically), which is so common, particularly in the older, uncontrolled diabetic, is essentially absent in early diabetics and in obese people, some of whom are potential diabetics.

No evidence was found to show that hypertension or retinal arteriosclerosis could be correlated with the obese patients' ability to use glucose. The incidence of hypertension appears to be higher in older diabetics. We believe, however, that this is essentially related to obesity and not to diabetes.

The proposal that diabetes in older people is commonly caused by sclerosis of the pancreatic blood vessels is discussed. Direct proof that sclerosis of the pancreatic vessels causes diabetes cannot be determined by clinical methods, nor can it be held responsible as a primary cause of diabetes when found at necropsy. Nevertheless, it seems improbable that such sclerosis can be regarded as a general cause for diabetes in older people.

BIBLIOGRAPHY

1. Bowen, B. D., Koenig, E. C., and Viele, A.: A study of the lower extremities in diabetes as compared with non-diabetic states, from the standpoint of x-ray findings, with particular reference to the relationship of arteriosclerosis and diabetes, Bull. Buffalo Gen. Hosp., 1924, ii, 35–41.
2. Joslin, E. P.: Arteriosclerosis and diabetes, Ann. Clin. Med., 1927, v, 1061–1080.
3. Bowen, B. D., and Koenig, E. C.: Arteriosclerosis and diabetes; including a roentgenological study of the lower extremities, Bull. Buffalo Gen. Hosp., 1927, v, 31–43.
4. Shepardson, H. C.: Arteriosclerosis in the young diabetic patient, Arch. Int. Med., 1930, xlv, 674–689.
5. Aschoff, L.: Introduction to "arteriosclerosis," E. V. Cowdry, 1933, Macmillan Co., New York, page 6.

6. LANSBURY, J., and BROWN, G. E.: Clinical significance of calcification of arteries of lower extremities, Proc. Staff Meet., Mayo Clin., 1934, ix, 49–55.
7. MASTER, A. M., and OPPENHEIMER, E. T.: Study of obesity. Circulatory, roentgen-ray and electrocardiographic investigations, Jr. Am. Med. Assoc., 1929, xcii, 1652–1656.
8. SMITH, H. L., and WILLIUS, F. A.: Adiposity of heart: clinical and pathologic study of 136 obese patients, Arch. Int. Med., 1933, lii, 911–931.
9. PINES, N.: Arterial hypertension and retinal changes, Brit. Jr. Ophth., 1927, xi, 489–522.
10. FRIEDENWALD, H.: Pathologic changes in retinal blood vessels in arteriosclerosis and hypertension, Trans. Oxford Ophth. Congr., 1930, I, 452–530.
11. MOORE, R. F.: Medical ophthalmology, 1922, P. Blakiston's Son and Co., Philadelphia.
12. FISHBERG, A. M., and OPPENHEIMER, B. S.: Differentiation and significance of certain ophthalmologic pictures in hypertensive diseases, Arch. Int. Med., 1930, xlvi, 901–920.
13. HARTMAN, H. R., and GHRIST, D. G.: Blood pressure and weight, Arch. Int. Med., 1929, xliv, 877–881.
14. DUBLIN, L. I.: Influence of weight on certain causes of death, Human Biol., 1931, 130. (Cited from SYDENSTRICKER, E.: Arteriosclerosis, E. V. Cowdry, 1933, Macmillan Co., New York, page 134.)
15. PREBLE, W. E.: Obesity: observations on one thousand cases, Boston Med. and Surg. Jr., 1923, clxxxviii, 617–621.
16. JOHN, H. J.: Hypertension and diabetes, ANN. INT. MED., 1932, v, 1462–1486.
17. RØMCKÉ, O.: Der Blutzucker im älteren Alter, insbesondere bei hypertonischen Zuständen. Zur Frage der chronischen Hyperglycämien mit normaler alimentärer Reaction, Acta med. Scandin., 1931, Supp. xxxix, 1–150.
18. MARSHALL, F. W.: Sugar content of blood in elderly people, Quart. Jr. Med., 1930–31, xxiv, 257–284.
19. SCHMIDT, and KYLIN: (Cited by Rømcké.[17])
20. HOPPE-SEYLER, G.: Beitrag zur Kenntnis der Beziehungen der Erkrankung des Pancreas und seiner Gefässe zum Diabetes mellitus, Deutsch. Arch. f. klin. Med., 1894, lii, 171–177.
21. HOPPE-SEYLER, G.: Über chronische Veränderungen des Pankreas bei Arteriosklerose und ihre Beziehung zum Diabetes mellitus, Deutsch. Arch. f. klin. Med., 1904, lxxxi, 119–162.
22. HERXHEIMER, G.: Zur Frage der Arteriolosklerose, Centralbl. f. allg. Path. u. path. Anat., 1923, xxxiii, 111–126.
23. BARRON, M.: Diseases of pancreas, Arch. Int. Med., 1925, xxxv, 807–817.
24. CECIL, R. L.: Discussion of SHEPARDSON, H. C.[4]
25. KRAUS, E. J.: Die pathologisch-anatomischen Veränderungen des Pankreas beim Diabetes mellitus, Handbuch der speziellen pathologischen Anatomie und Histologie, 1929, 622–747.
26. WARREN, S.: Pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia, page 58.
27. PETERSON, R. F.: The relation of hypertension and arteriosclerosis to diabetes mellitus. A thesis submitted to the faculty of the Graduate School, the University of Minnesota, 1927.
28. ROSENTHAL, S. R.: Studies in atherosclerosis: chemical, experimental and morphologic. III and IV: Rôles of cholesterol metabolism, blood pressure and structure of aorta; fat angle of aorta (F.A.A.), and infiltration-expression theory of lipoid deposit, Arch. Path., 1934, xviii, 473; 660–698.
29. ENKLEWITZ, M.: Diabetes and coronary thrombosis, Am. Heart Jr., 1934, ix, 386–395.

STUDIES RELATING VITAMIN C DEFICIENCY TO RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS; EXPERIMENTAL, CLINICAL AND GENERAL CONSIDERATIONS *

II. RHEUMATOID (ATROPHIC) ARTHRITIS

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A border-land between rheumatic fever and rheumatoid arthritis has long been recognized. Particularly in young adults clinical distinction may prove difficult or one may find an apparently typical rheumatic fever with carditis progress into a characteristic rheumatoid arthritis. Klinge and Grzimek [1] find that although acute and subacute rheumatic fever and chronic polyarthritis are usually easily differentiated, both disease pictures are so closely bound together in the arthritic and general pathology that a "rheumatic" basis may be assigned to both. Dawson [2] has lent further support to the concept of a relationship of the two diseases in showing that the early pathological change found in the subcutaneous nodules of rheumatic fever and rheumatoid arthritis, are essentially identical. This evidence, together with encouraging early observations made on the joints in scurvy [3, 4] led to a rather extensive study of the scorbutic arthropathy. It is the purpose of this paper to report the findings of this study and to draw attention to a rather convincing amount of data suggesting that vitamin C undernutrition may be an etiological factor in at least some of the cases classified as rheumatoid arthritis.

EXPERIMENTAL METHODS

The methods employed consisted briefly in maintaining guinea pigs for rather prolonged periods of time on a basic vitamin C free diet,† supplemented with inadequate amounts of vitamin C. To study the influence of infection, parts of each experimental series were infected. Control groups

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The first part of Dr. Rinehart's article appeared in the preceding number of the ANNALS.

† The basic diet used is as follows:

	Per cent
Ground rolled oats and bran—equal parts by volume	56
Powdered skimmed milk (baked at 110° for 2 hours)	30
Butter fat	10
Sodium chloride	0.5
Osborne-Mendel salt mixture	1.0
Dried yeast	1.5
Cod-liver oil (standardized)	1.0

Care is used in securing a thorough mixture of the above ingredients. Guinea pigs eat this diet well and, with adequate vitamin C supplement, grow and thrive.

of course, were maintained on the basic diet adequately supplemented with vitamin C and subjected to the same infection. The material of this study comprises 12 series of experiments. Inasmuch as pathological observations are in essential agreement in the various experiments, no attempt will be made to report individual experiments. Sufficient detail will be found in the appended protocols, to guide anyone interested in repeating the experimental work. No sharp line can be drawn between the experiments pertaining to rheumatic fever and to the chronic arthritis. An over-lapping occurs here as is observed clinically.

The Arthritis of Subacute or Chronic Scurvy

One of the first objective manifestations of vitamin C deficiency in the guinea pig is an arthropathy which is characterized by pain, swelling and limitation of movement in multiple joints. The joints exhibiting the most obvious involvement, and the usual, though not invariable sequence, are

Fig. 1. Diffuse fusiform swelling of the wrists, an early manifestation of vitamin C deficiency in the guinea pig.

knees, wrists, and elbows. These have been most carefully studied, but it is probable that no joints are immune. Figure 1 illustrates a characteristic appearance of an early arthritic change with a fusiform swelling about the wrists.

The Early Changes in Scorbutic Arthropathy

An exhaustive study has not been made of the earliest changes in the scorbutic arthritis. However, joints of several animals have been inspected shortly after the onset of stiffness and swelling. The periarticular tissues are seen to show an edematous, hemorrhagic appearance. Microscopically, red blood cells and serum are found, spreading apart connective tissue cells, and frequently, relatively broad hyaline streaks of a peculiarly packed fibrin are seen. At this time or shortly later, the connective tissue cells begin actively to proliferate, the hemorrhagic appearance subsides and we see an imperfectly vascularized and frequently edematous granulation tissue thickening the capsule and obscuring the underlying tendons and bony prominences.

The Arthropathy of Subacute or Chronic Scurvy

A much more extensive material has been studied in the later stages of the scorbutic joint disability. For convenience and clarity, it is best to consider separately the changes in the various anatomical structures forming and surrounding the joint.

Synovial Proliferation and Pannus Formation. A proliferative reaction of the synovial membrane is an almost constant finding. Usually associated with the synovial proliferation and frequently merging with the proliferating cells is a hyaline "fibrinoid" material. Figure 2 illustrates a typical reaction of this type. No sharp distinctions can be drawn between cells clearly recognizable as synovial and less differentiated connective tissue cells which, intermingled with the fibrinous material, extend from joint recesses as long tongue-like processes into the joint cavity and over the articular surfaces. Figure 3 shows the detail of such a fibrous and "fibrinoid" pannus.

Subsynovial and Peritendinous Lesions. The connective tissue beneath the synovial membrane and that about the tendons inserting around the joint present analogous changes. Here again, small extravasations of blood, streaks of fibrin and a reactive hyperplasia of connective tissue cells contribute further to the swelling deformity and limitation of movement in the joint.

Articular Cartilage. In addition to diffuse thinning, a retrogressive change, apparently a de-differentiation of areas of the articular cartilage, is not uncommonly seen. In places the surface of the articular cartilage is replaced by undifferentiated and at times vascularized connective tissue. The pannus described is, in some instances, adherent to the articular surfaces. The retrogressive change at the surface of the articular cartilage and apparent "perichondral" proliferation are shown in figure 4.

Rarefaction of Bone. Thinning of bone trabeculae is characteristic of chronic vitamin C deficiency. This rarefaction of bone involves apparently the entire skeleton but is most prominent at the bone ends. The change is

FIG. 2. A moderately intense proliferation of the synovial membrane from a recess in the knee joint of a guinea pig subjected to a subacute vitamin C deficiency and infection (beta streptococcus). × 200.

clearly evident in microscopic sections (figure 5), and has been repeatedly demonstrated by roentgen-ray examination. Figure 6 illustrates this change.

Muscle. Some degree of muscle atrophy and degeneration is also a characteristic effect of prolonged vitamin C deficiency. An interstitial edema of the muscle is frequently seen to contribute to the periarticular swelling. In some of the more severe deficient states, hemorrhagic stippling of the muscle may occur. Some degree of muscle atrophy or degeneration is almost regularly found. Occasionally a widespread muscle degeneration dominates the pathologic picture. It would appear that this occasional severe myopathy is an effect of capillary hemorrhage and consequent cellular anoxemia.

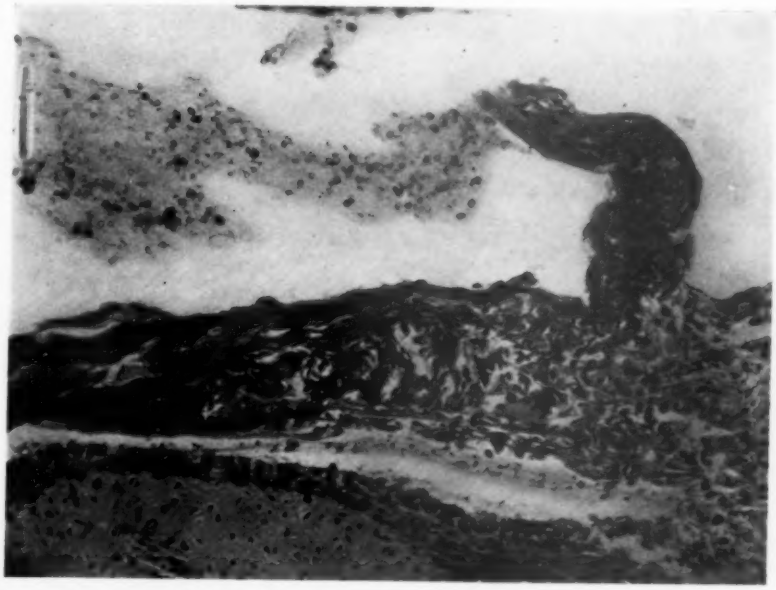

FIG. 3. Fibrous and "fibrinoid" pannus extending from a joint recess of the knee over the articular cartilage. Relatively acute scurvy and bronchopneumonia (*B. bronchisepticus*). The fibrinous material shows as grayish-black lines in microphotograph. × 200.

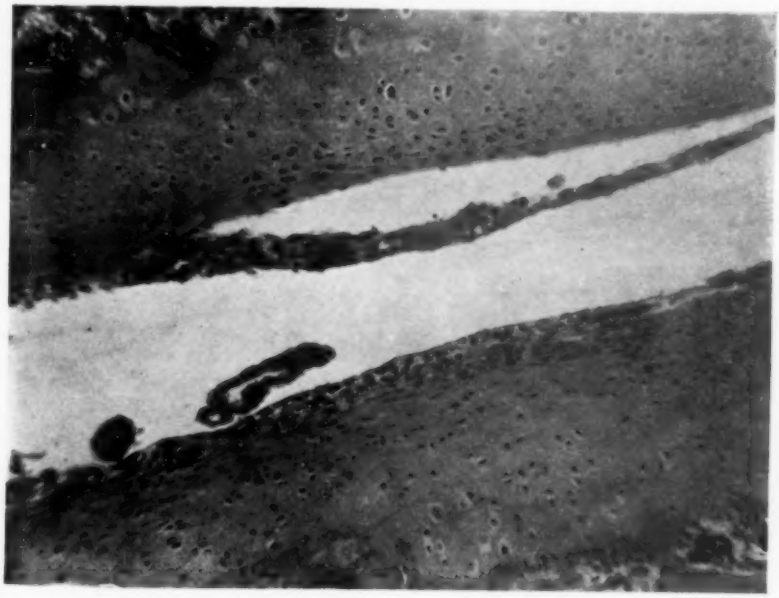

FIG. 4. Showing a retrogressive change in the articular cartilage, a dedifferentiation of the surface cells at one side and an apparent perichondrial proliferation with an associated fibrinous material at the opposite surface. Subacute scurvy and infection—duration 48 days. Developed spontaneous bronchopneumonia (*B. bronchisepticus*) on the twenty-fifth day. × 200.

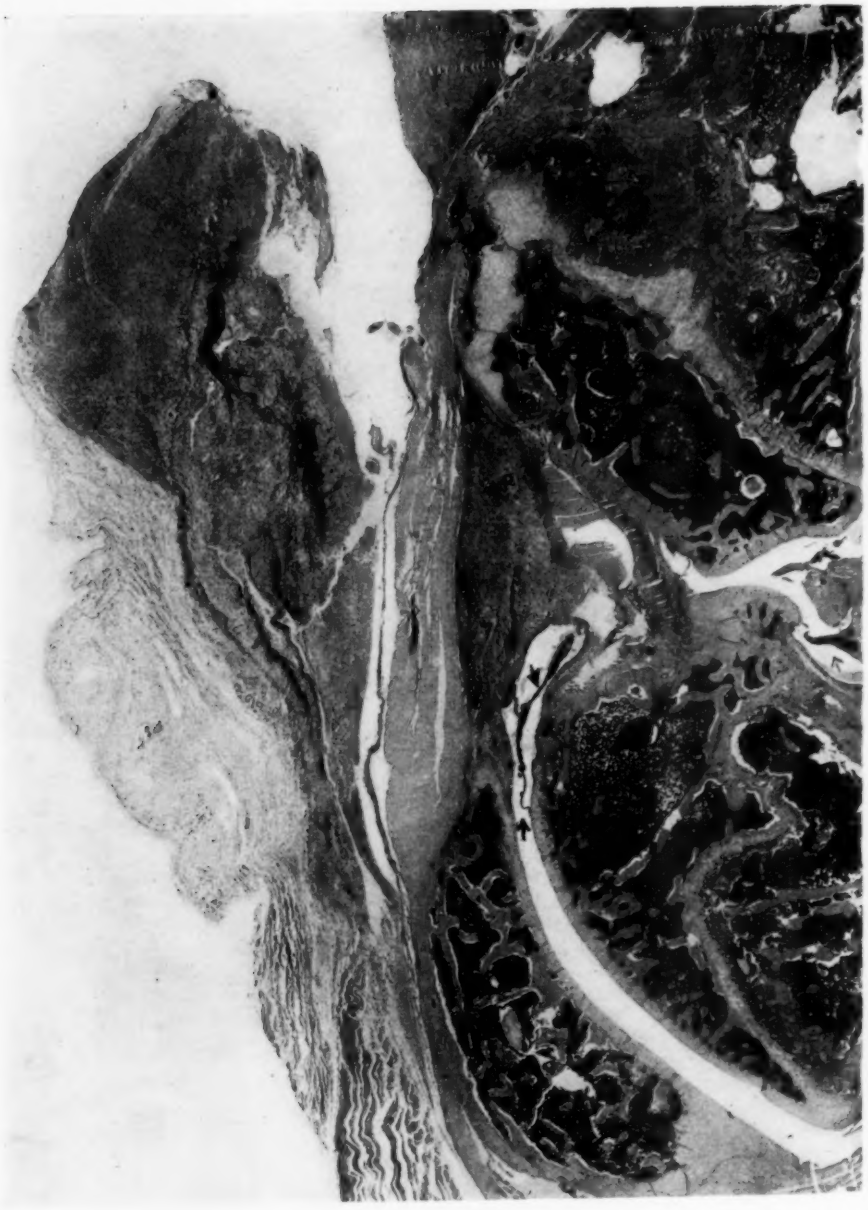

FIG. 5. Showing in low magnification the characteristic changes in the scorbutic arthropathy. The early pannus extending from joint recesses is indicated by the arrows. The thinning of the bone trabeculae may be seen, and the marked capsular thickening is evident. × 18.

Periarticular Reactions—Subcutaneous Nodules. The reactions in the capsular tissues are, perhaps, of greatest interest. The early sanguinous edema has been noted. Somewhat later, the capsular connective tissue undergoes a marked proliferative reaction. Commonly, streaks of hyalinized fibrin lie in intimate association with the reactive connective tissue. The tissue, on section, often shows a striking edema. Somewhat later, a

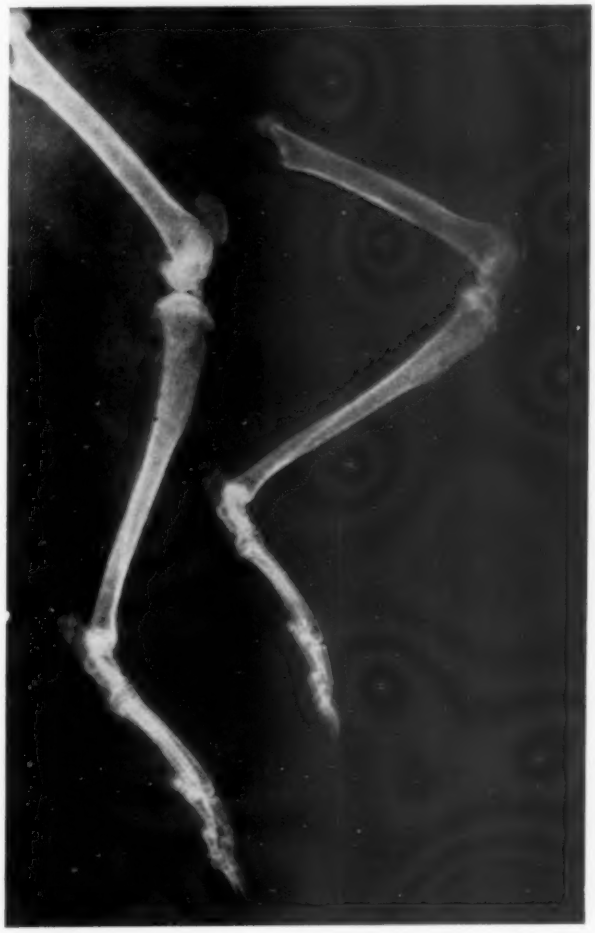

FIG. 6. This x-ray shows the hind leg of a control animal on the left, contrasted with a vitamin C deficient animal on the right. The excised limbs were exposed simultaneously; both were in an extended position. The limitation of extension is apparent in the scorbutic joint. The diminished density of the scorbutic bone, particularly at the ends about the knee joint, is clearly shown. This observation has been repeatedly verified.

gradual diminution of the periarticular thickening may occur, coincident with the shrinkage of the connective tissue. Figure 5 illustrates the topography of the intra- and periarticular lesions. A most interesting observation is the not infrequent development of discrete circumscribed fibrous

tissue nodules beneath the skin about the joints. Sometimes they are moveable beneath the skin and at other times are found more or less attached to an underlying bony prominence. The knee joint shown in figure 7 shows two such subcutaneous fibrous nodules as well as the thickening and deformity of the joint produced by scurvy. The position of the joint shows the limitation of extension. Microscopic sections of the subcutaneous nodules show an edematous, cellular, fibrous tissue, usually associated with

FIG. 7. A striking scorbutic arthropathy knee joint photographed in an extended position, showing limitation of extension, diffuse fibrous tissue thickening about the joint and two fibrous subcutaneous nodules. Uncomplicated vitamin C deficiency. Duration of experiment—70 days. Degree of deficiency, moderately severe.

irregular strands of brilliantly eosinophilic hyalinized fibrin (figure 8). The hyaline fibrin is in intimate association with connective tissue cells, and appears to correspond to the "fibrinoid" degeneration of Klinge.[5] The experimentally produced subcutaneous nodules resemble most closely the pathologic picture of the subcutaneous nodules of rheumatic fever and the earlier nodules of rheumatoid arthritis, excellently described and illustrated by Dawson.[2]

THE EFFECT OF INFECTION SUPERIMPOSED ON THE CHRONIC SCURVY

The arthritic pathology described occurs in the absence of any introduced or demonstrable infection. Some infections, however, have been found to accentuate and accelerate the pathological process. This influence is clearly shown in the following experiment.

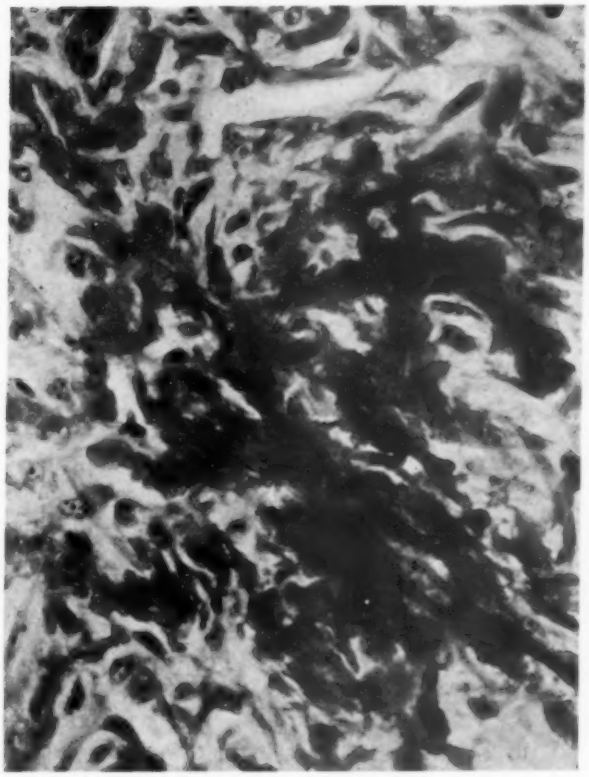

FIG. 8. A portion of an experimental subcutaneous nodule developed in an animal subjected to chronic vitamin C deficiency and infection. Streaks of a brilliantly eosinophilic hyalinized fibrin together with a reactive hyperplasia of imperfectly vascularized connective tissue constitutes the structure of this lesion, and corresponds closely to the rheumatic nodule. × 400.

Experimental Series 14.

Nov. 1, 1934: A group of 13 animals were placed on the basic diet with an adequate daily supplement of orange juice (4 c.c.). The animals were in groups in three cages. Nov. 23, 1934: One animal in a cage of five developed a spontaneous respiratory infection, which was later determined to be due to *B. bronchisepticus.* Four days later, four other animals in the cage developed the same type of infection. Eight other animals in two other cages showed no evidence of infection. At this stage, five non-infected animals were placed in a larger cage with the four infected animals, and the group was transferred to a separate room. Of these animals, five were placed on a scorbutic régime, and four continued to receive 5 c.c. orange juice daily. Four animals were maintained unexposed to infection and subjected to the same scorbutic régime. In this instance, the scorbutic régime consisted of total deprivation of vitamin C for 18 days beginning Nov. 29, then a supplement of 1 c.c. on alternate days for 16 days, when the experiment was concluded. The five scurvy and four control animals in the infected cage all showed evidence of pulmonary infection. The scurvy animals exposed to infection all developed frank arthritic manifestations in from 10 to 15 days with an average time of onset 13 days after the deprivation of vitamin C. The non-infected scorbutic animals in this series showed

no arthritic manifestations for periods of 24 to 32 days, with an average time of onset of 31 days. Further, the arthritic manifestations in the group exposed to both scurvy and infection were clearly more severe than those subjected to scurvy alone. The animals exposed to the infection, but given an adequate orange juice supplement, although developing infection, showed no arthritic manifestations.

It would appear quite evident that the infection, in this instance, augmented the scorbutic effect in development of the arthritic lesions. Essentially similar observations have been made with other experimental infections. In other instances, however, this has not been apparent. It would seem that the type and virulence of the infection are of importance in this relationship.*

Summary of the Pathological Changes in the Scorbutic Arthropathy

The arthritis of subacute or chronic scurvy, uncomplicated or with superimposed infection, is characterized within the joint by synovial proliferation and "fibrinoid" and connective tissue pannus formation. The capsular, peritendinous and intermuscular tissues show fibrin deposition, and reactive hyperplasia of an imperfectly vascularized connective tissue. These changes contribute to pain, swelling and limitation of movement or effectual ankylosis in multiple joints. Striking lesions, frequently observed, are subcutaneous nodules histologically characterized by streaks of fibrin and reactive hyperplasia of connective tissue, and bearing a close resemblance to "rheumatic" nodules. Muscle atrophy and degeneration are regularly observed in the scorbutic arthritis. A general skeletal rarefaction develops, which is most marked at the bone ends. Certain infections accelerate and intensify the arthritic process, while others do not.

Representative Protocols

Series 7. No. 189. Received basal diet plus adequate orange juice supplement for 15 days. 6/1/33 to 6/8/33, no orange juice. 6/8/33 to 6/20/33, 1 c.c. daily. 6/21/33 to 6/26/33, 0.5 c.c. daily. 6/27/33 to 7/16/33, 1 c.c. daily and 7/16/33 to 8/2/33, 0.5 c.c. daily. On 6/16/33 the animal was infected by inoculation of a broth culture of beta streptococcus (source spontaneous lymphadenitis of guinea pig). The inoculation was made into the skin of the left groin, and the animal developed a local skin infection and lymphadenitis. *Course:* 6/24/33, the left knee is stiff with limitation of extension; four days later, the right knee also stiff. 7/21/33, both knees are stiff and swollen. 7/25/33, the elbows are also swollen. 8/2/33, animal sacrificed. *Pathological notes:* General nutrition is fair. The mucous membrane of the bladder is hemorrhagic. A small abscess is present

* A few observations suggest that vitamin C deficiency may produce in the joints a locus of diminished resistance to the actual lodgement of bacteria and so predispose to the development of a truly infectious (suppurative) arthritis. This is illustrated by an observation on a guinea pig in Experimental Series Number 12. This animal was in a group subjected to chronic vitamin C deficiency, but had exhibited swelling of joints, particularly of one knee, that was much more marked than in the other members of the series. The temperature was elevated. At autopsy, an acute suppurative arthritis was evident in the most swollen knee. Cultures of the spleen and inguinal lymph node yielded a green streptococcus.

between the liver and the diaphragm. A little hemorrhage is seen over and under the right knee. This joint shows capsular thickening, synovial proliferation and early pannus formation.

Series 8. No. 201. This animal was one of a group subjected to vitamin C deficiency for a period of approximately 41 days. These animals received 1 c.c. of orange juice three times a week during the course of the experiment. Weight at onset of the experiment, 8/17/33, 374 grams. *Course:* 9/14/33, slight thickening of the tissues about the knees first noted. 9/20/33, slight stiffness and thickening of the knees, no swelling. 9/28/33, weight, 248 grams. Knees thickened and stiff. Animal sacrificed. *Pathological notes:* Moderate thickening of the capsule of the right knee. Moderate congestion and hemorrhagic stippling of the bladder mucous membrane.

Series 8. No. 210. This animal was one of a group in the same experiment subjected to the same dietary régime but also to infection with a hemolytic staphylococcus. This animal as the others of the group showed a more marked arthropathy than the animals subjected to scurvy alone, even though the local reaction at the site of infection was quite mild. *Course:* 9/14/33, knees stiff and slightly thickened. On this date the animal was infected by intracutaneous inoculation with a broth culture of hemolytic staphylococci into the skin of the neck. A mild non-suppurative cervical adenitis resulted. 9/20/33, the right knee is definitely swollen. 9/28/33, both knees thickened, stiff and swollen. Animal sacrificed. Some hemorrhage in chest wall. Right knee shows considerable capsular thickening composed of a brownish granulation tissue. There are areas of hemorrhage in this tissue. The muscle below the knee appears edematous and shows some recent hemorrhage.

Series 9. No. 247. This animal was placed on the basal diet 10/25/33. For the first 20 days a total supplement of 8 c.c. of orange juice was given. At this time, 11/15/33, the animal exhibited swelling and stiffness of both knees and tenderness of the wrists. For the next two and one-half months, the animal received alternately adequate and inadequate amounts of orange juice, the average daily intake being 1.7 c.c. Infection was introduced (beta hemolytic streptococcus) into the skin of the neck on 12/17/33. After 2/7/34, the animal received 1 c.c. of orange juice daily until death on 4/30/34, approximately six months after the onset of the experiment. *Course:* The general nutrition of the animal remained fair, and more or less arthritic disability was present in the knees, wrists and elbows throughout the experiment, with several episodes of swelling. *Pathological notes:* At autopsy, a fibrous nodule was found near the left elbow. The knee and elbow joints on section showed bone atrophy and synovial proliferation. The elbow in addition showed irregularity of the articular surface and apparent perichondrial proliferation. The subcutaneous nodule showed hyalin streaks of fibrin and reactive hyperplasia of the connective tissue.

Series 15. No. 368. Animal placed upon basal diet 11/20/34, and maintained with an adequate daily supplement of orange juice (4 c.c.) to 12/4/34, when the supplement was entirely removed for 13 days. Then animal received orange juice 1 c.c. on alternate days until 1/7/35 when sacrificed. *Course:* The temperature record indicated that the animal had developed a spontaneous infection about 12/14/34. Swelling of the knees was noted 12/15/34. On 12/24/34 the knees were swollen and tender, and the elbows were tender. *Pathological notes:* Autopsy revealed an extensive bronchopneumonia (*B. bronchisepticus*). The costochondral junctures were moderately thickened. The capsular tissues of the right knee were distinctly thickened with a brownish-red granulation tissue. There was no evidence of fresh hemorrhage. A protruding nodule of granulation tissue was found at the inner aspect of the right elbow. Sections of the knee

showed fibrous and fibrinous pannus, buckling of the cartilage and fibrous tissue thickening of the capsule. The elbow showed a broad fibrinous and fibrous tissue pannus.

Series 15. No. 376. Same series and dietary régime as 368, without however any evidence of infection. The animal survived until sacrificed on 1/31/35. *Course:* General condition and nutrition remained good. The animal first developed tenderness of knees without any swelling on 12/14/34. On 12/21/34, the knees were tender and slightly swollen, and the left wrist was swollen and tender. No elevation of temperature. On 1/31/35, the animal showed stiff, thickened and tender knees with subcutaneous nodules on both knees (see photograph in text). *Pathological notes:* The left knee showed diffuse fibrous tissue thickening of the capsule, with in addition two subcutaneous nodules. The periarticular tissues were edematous and congested. The right knee showed a similar appearance. One subcutaneous nodule was present. The capsular tissue of the right knee was 1 mm. thick. The left wrist also showed periarticular thickening.

Fundamental Similarities of the Experimental Lesions to Those of Rheumatoid Arthritis

One familiar with the pathology of rheumatoid arthritis will at once recognize certain basic similarities of the experimental arthritis described, to this condition. The study of Nichols and Richardson,[6] on the pathology of chronic arthritis, remains a classic. Particularly with respect to rheumatoid arthritis, relatively little has been added to their original observations. The work of Fisher[7] has served to confirm and in some respects extend their observations. The essential changes can be no more clearly or succinctly given than in the words of Nichols and Richardson, who in referring to proliferative arthritis (rheumatoid) say: "In this type of joint lesion the primary change occurs as a proliferation of the synovial membrane and the perichondrium of the articular cavity, combined in many cases with a synchronous proliferation of the connective tissue and the endosteum of the epiphyseal marrow directly below the joint cartilage"; and further: "The proliferation and extension over the surface of the cartilage of the synovial membrane is the earliest and most marked feature of these joints. The pannus may be composed of a very vascular granulation tissue infiltrated with lymphoid and plasma cells, with comparatively little intercellular material or may be a very dense fibrous tissue with very few vessels and no obvious infiltration." Of the periarticular and capsular tissues they state: "In all cases of proliferative arthritis changes occur in the capsule, usually synchronous with changes in the synovial membrane. This change consists in a proliferation of the connective tissue of the capsule and leads to a greater or less thickening usually of the entire capsule." They note that in the early stages, there may be a connective tissue with little intercellular substance which later becomes denser with more or less hyalinization and vascular obliteration. In both stages the tissue may or may not be infiltrated with lymphoid and plasma cells. Fisher's observations are in essential agreement. In addition, he notes that in the more central parts of the articular cartilage one may often find shallow ulcers whose floor is formed by connective tissue

formed by metaplasia of the superficial cartilage cells. In the later stages of the disease the extreme fragility of the affected bones is noted. Llewellyn and Jones [8] have suggested substitution of the term fibrositis for chronic rheumatism, because they consider the basic anatomic lesion is one of inflammatory overgrowth, or hyperplasia of the white fibrous connective tissue. They further point out that, in chronic articular rheumatism, the periarticular, subsynovial and ligamentous tissues are at times more often and more deeply affected by the morbid process than the synovial or bony elements. Emphasis is also placed upon the importance of muscular degenerations in the rheumatic syndrome. Klinge and Grzimek's [1] studies indicate the importance of the "fibrinoid" degeneration in this type of arthritis as well as in rheumatic fever. The essential identity of the anatomic lesion in the experimentally produced subcutaneous nodules and those of rheumatic fever and rheumatoid arthritis has been noted. Considerable significance is attached to the experimental occurrence of this lesion because of its unusual character. Many observers have stressed the bone atrophy accompanying rheumatoid arthritis. Indeed, this change formed the basis for the classification of the disease as atrophic arthritis by Goldthwait.[9] Swaim [10] has noted the atrophy of the whole bony system in this type of arthritis. Howitt and Christie [11] emphasize the importance of the general progressive skeletal atrophy which they find demonstrable, before the onset of joint changes.

Summary of the Pathological Similarities between Scorbutic and Rheumatoid Arthritis

It will be seen that there are many pathologic similarities between the experimental scorbutic and rheumatoid types of arthritis. Features in common include synovial proliferation and connective tissue pannus formation. In the capsular and periarticular tissues, connective tissue overgrowth is seen in both conditions. The hyaline streaks of fibrin usually found in association with the connective tissue hyperplasia of scorbutic arthritis, appear to correspond with the "fibrinoid" degeneration, which Klinge finds to be a basic lesion in the rheumatic diseases. Retrogressive changes in the articular cartilage are observed in both scorbutic and rheumatoid arthritis. In a few instances, fibrous tissue transformation of the subarticular marrow, noted by Nichols and Richardson in proliferative arthritis, has been seen in the scorbutic joints. General skeletal atrophy, most marked at bone ends, is seen in both the experimental and clinical arthritis. Muscle atrophy and degeneration occur in both conditions. Finally, fibrous nodules develop beneath the skin in experimental animals, that are remarkably like the early subcutaneous nodules of rheumatoid arthritis. One microscopic feature commonly but not constantly observed in rheumatoid arthritis is the presence of focal collections of lymphocytes in and about the synovial tissues. This change has been seen in only a few instances in the scorbutic joints and has never been a prominent feature. It is possible that if a more chronic process were produced experimentally, this lesion might be observed.

Discussion

Scattered reports have directed attention to joint disabilities in the presence of vitamin C deficiency. Jackson and Moore [12] noted the prominence of joint manifestations in guinea pigs fed an exclusively milk diet. Smith [13] observed that the first manifestations of scurvy in guinea pigs are swollen and tender joints. The diet employed by her consisted of a paste made of alfalfa meal and wheat flour with whole oats and water given *ad lib.* Howe [14] fed guinea pigs rolled oats and fat free milk supplemented with small amounts of carrot and lettuce. By regulating the intake of carrots and lettuce he maintained the animals in a deficient state for periods of three months to a year. His interest was primarily in dental degenerative changes, but he states: "The usual joint affections occur to a marked degree, and when this condition has been maintained for a long time and the animals are restored to a normal diet, it is found that the legs have become fixed in an abnormal position. This seems to us to be more like rheumatism and arthritis deformans than many experimental conditions that have been called such." Stiner,[15] in a paper entitled "Experiments on Rheumatic Diseases in Animals," observed that young guinea pigs fed sterilized food (e.g., hay, turnips, oats) and various kinds of prepared milk, developed joint swelling, disability and deformity. He recognized the vitamin C deficiency of the diet but was also inclined to ascribe a direct noxious effect to the pasteurized milk. He was impressed by the general similarity of the manifestations in the animals to the manifestations of rheumatism in man. It will be recognized that the experimental diets employed by the investigators cited are probably deficient in other food factors than vitamin C, including salts and other vitamins, although the outstanding deficiency was certainly of vitamin C.

General Considerations

Many of the epidemiological factors, previously considered,[16] which apply to rheumatic fever, pertain also to rheumatoid arthritis. The evidence indicating the existence of latent scurvy and the factors relating to storage and utilization of vitamin C are equally pertinent. The observations suggesting that the vitamin C requirement may be enhanced by achlorhydria would appear significant in view of the relatively high incidence of this factor in rheumatoid arthritis. The data cited, indicating the depleting effects of fatigue and certain infections on the organic stores of vitamin C, suggest auxiliary mechanisms that might precipitate a significant deficiency state.

The impaired peripheral circulation, emphasized by Pemberton and Osgood [17] in rheumatoid arthritis, would appear explainable on the basis of vitamin C deficiency. The pathology of chronic scurvy is dependent, to a considerable extent, upon the impairment of the capillary wall and attendant circulatory inadequacies.

The importance of acute infections and of focal infection, emphasized

particularly by Cecil [18] and his school, is not denied. Indeed, the experimental data strongly suggest that certain infection may accelerate and aggravate the scorbutic arthritis, and in some instances, it would appear that the deficiency may, by lowering the resistance of the joint tissues to circulating bacteria, favor their lodgement and the development of a truly infectious (purulent) arthritis. Milder infections might occur with less virulent organisms.

Howitt and Christie [11] direct attention to the prodromal symptoms frequently preceding the onset of rheumatoid arthritis. These include loss of appetite, tachycardia, fall in blood pressure, a slightly raised temperature, sweating of the hands and feet, dermatographia, tremor, nervousness, loss of weight, an extreme degree of fatigue, disability, and vague muscular pains. It would seem significant that many of these symptoms are characteristic of latent scurvy.

There is a definite tendency among students of the subject, to consider rheumatoid arthritis a general constitutional disease with joint manifestations as its most serious feature. This is clearly evidenced by the reports of the American Committee for the Control of Rheumatism [19] and of the Committee of the British Medical Association [20] as well as by numerous individual studies. The general atrophic changes often encountered in rheumatoid arthritis, involving skin, hair, fingernails, muscles and bony skeleton, have been particularly noted by Swaim.[21] Swollen, puffy, edematous gums are frequently seen in this disease. Swaim [21] observes: "The gums are spongy and teeth decay easily. The mouth resembles that of a scurvy patient."

Many writers have stressed the importance of nutrition, notably Goldthwait,[22] Burnett and Ober,[23] Howitt and Christie,[11] Irons,[24] Fletcher,[25] Pemberton,[26] Rowlands [27] and Hall.[28] The latter notes: "We are constantly seeing patients with severe arthritis, who for months or years have been eating inadequate or deficient diets. In such cases, the diet has been the depleting factor." Rowlands,[27] and Fletcher and Graham [29] have presented indirect evidence that vitamin B deficiency may operate in the etiology of rheumatoid arthritis. The evidence is based essentially upon the frequent observation of atony of the musculature of the colon. Fletcher and Graham gave patients high vitamin diets with particularly generous amounts of vitamin B and observed improved tone in the bowel and frequently much clinical benefit. It is not improbable that vitamin B deficient states do indirectly contribute to development of arthritis. Nutritional inadequacies are likely to be multiple. Vitamin B deficiency appears to act largely through limitation of the voluntary food consumption by impairment of appetite. In this way, an inadequate vitamin C intake might follow in its wake, particularly if the food selection did not include the richer sources of this factor.

Although it is not the primary purpose of this paper to report clinical studies of rheumatoid arthritis which are in progress,[30] certain general facts

have emerged which appear worthy of comment. In the first place, careful inquiry into dietary habits of persons suffering from this disease has indicated that a very considerable number have been on faulty diets, and in many instances, surprisingly low in vitamin C containing foods. Further, capillary resistance tests (an index of latent scurvy) have shown, in general, low levels, and with the institution of high vitamin C containing diets, these levels have risen. Several cases reported here exemplify these findings.

Case Reports

Case 1. S. T. B., white male, aged 42. On January 15, 1934, the patient thought that he had sprained his right ankle. The next morning, he found his knees, elbows, wrists and ankles were stiff. The left knee was considerably swollen and the other joints less so. He entered the San Francisco Hospital, Febr. 10, 1934, showing moderate swelling and pain in wrists, knees and the right ankle. Study of his dietary habits revealed striking inadequacies for several years due to unemployment. Cracked oats, bread, coffee, beans and stews formed the bulk of his foods. Just preceding the onset of arthritis, the diet had been somewhat more generous but still low in vitamin C. More than usual physical work and exposure immediately preceded the onset of arthritis. Capillary resistance tests (Dalldorf method) gave low readings. The dental condition was extremely bad with reddened, edematous gums. The patient was given the routine hospital diet with a daily supplement of one quart of orange juice. Improvement was rapid and recovery complete without further therapy. Four months later, the patient was found to have remained asymptomatic. The capillary resistance level had returned to normal.

The presence of vitamin C deficiency here can hardly be doubted. In fact, it appears that the patient probably suffered a scorbutic arthritis which, however, was clinically considered to be an early, relatively acute, rheumatoid type of arthritis.

Case 2. C. H., white female, aged 42, entered University of California Clinic, January 1, 1934, with a complaint of pain and swelling of right foot and ankle for past eight months. At the onset, she had an attack of pleurisy. Transient pains appeared in her elbows and ankles. A few days later, the pain in the left ankle became very severe. At about the fourth week, the ankle was said to be of a bluish-red color. At the clinic, the ankle showed a diffuse hard swelling with a yellowish area of discoloration at the medial aspect. Roentgen-ray examination revealed marked atrophy of the bone about the ankle joint. The roentgen-ray diagnosis was acute infectious arthritis. Diet analysis by an experienced nutritionist revealed a low intake of vitamin B and what was considered a very low intake of vitamin C. The capillary resistance test showed a surprisingly low strength. The ankle was placed in good position in a light ambulatory splint, and the patient returned to her home with diet instructions to supply a very generous amount of vitamin C. One month later, excellent improvement in the condition of the ankle was noted. The capillary resistance showed a moderate but definite elevation. A report of recent date indicates little or no residual disability.

Case 3. A. H., white male, sailor, aged 45, entered U. C. Hospital, March 1, 1935, with a typical erythema multiforme and a mild arthritis, dating back two weeks. On entry, examination showed swelling of knees with excess fluid, and some limitation of movement in shoulder. Dietary inquiry revealed generous and apparently adequate food intake including vitamin C up to five months ago, when the patient lost his job as

a merchant sailor. Since that time, the patient had been on relief, receiving a small cash allowance. He prepared his own food. The caloric intake was relatively generous, but except for potato, practically no vitamin C-containing foods were consumed. He ate little or no fresh fruit or vegetables in this period. Capillary resistance tests were considered within normal limit. Oral hygiene was poor, and the gums were puffy, red and edematous. On March 3, 1935, the patient was started on daily doses of sodium ascorbate (250 mg.) intravenously. The following day, the left wrist was painful to movement, and there was thickening over the first metacarpal phalangeal articulation. The erythema showed evidence of clearing. March 7: Pain and swelling in knees were subsiding, and the wrist pain had gone. Progressive clinical improvement ensued, which has persisted to date, in spite of the fact that a suppurative inguinal lymphadenitis has developed. At the present, five weeks after entry, the skin is clear and patient is free of arthritis. The general condition is improved and gums appear firmer. The patient was given 7 daily doses of sodium ascorbate (250 mg. each) intravenously, then doses three times a week for three weeks, following which he was advised to eat vitamin C-containing foods.

Case 4. L. H. F., male, aged 34. This patient is one who had a chronic arthritis of the rheumatoid type with marked disability and deformity. A more or less progressive development dated back to an onset 16 years previously. Dietary habits indicated a moderately but not severely low intake of vitamins B and C-containing foods. Capillary resistance tests gave strikingly low readings. The gums were puffy, reddened and retracted. The arthritic disability consisted in stiffness, deformity and pain in hands, wrists, elbows, feet and ankles. The patient was instructed to take one pint of orange juice daily. He has been on this régime for 15 months. Gradually the capillary resistance has returned to a nearly normal level at present. Although improved, it was distinctly low six months after onset of dietary régime. Although he has had recurrent attacks of pain in one or more joints, the painful episodes are distinctly less frequent and less severe. The patient considers his general sense of well being and arthritic condition distinctly improved.

The writer does not wish to be guilty of the single-minded zeal warned against by Pemberton.[31] Indeed, he is in complete sympathy with a broad, unbiased approach to the problem, and realizes that many factors, some known, others not, lie in the background. It is felt, however, that the evidence indicates that vitamin C deficiency may operate as an important factor in the etiology of some cases of rheumatoid arthritis, and that the concept is worthy of serious consideration.

Summary and Conclusions

Subacute or chronic vitamin C deficiency in the guinea pig produces an arthropathy with manifold similarities to rheumatoid arthritis. These include synovial proliferation, intra-articular pannus formation, periarticular fibrous tissue overgrowth, bone atrophy and subcutaneous nodules. In certain instances, superimposed infection accelerates and accentuates the pathological process. In this study, infection in the presence of adequate vitamin C nutrition failed to produce arthritis. Brief evidence is presented that vitamin C deficiency may, by producing a locus of diminished resistance, also operate as a predisposing factor in the etiology of truly infectious (suppurative) types of arthritis. The general atrophic changes found in rheumatoid arthritis involving bony skeleton, muscle and skin, are seen also in

chronic vitamin C deficiency. Evidence indicating the probable clinical importance of latent scurvy, and the depleting effect of fatigue and certain infections on the organic stores of vitamin C, is noted. Clinical data are cited that the nutritional habits are frequently imperfect preceding the onset and during the course of rheumatoid arthritis. Experimental, epidemiological and clinical evidences afford the basis for the concept presented, that vitamin C deficiency may operate as a factor in the etiology of some cases classified as rheumatoid arthritis.

REFERENCES

1. KLINGE, F., and GRZIMEK, N.: Das Gewebsbild des fieberhaften Rheumatismus. VI. Mitteilung. Der chronische Gelenkrheumatismus (Infektarthritis, Polyarthritis lenta) und über "rheumatische Stigmata," Virchow's Arch. f. path. Anat., 1932, ccxxciv, 646–712.
2. DAWSON, M. H.: A comparative study of subcutaneous nodules in rheumatic fever and rheumatoid arthritis, Jr. Exper. Med., 1933, lvii, 845–858.
3. RINEHART, J. F., CONNOR, C. L., and METTIER, S. R.: Further observations on pathologic similarities between experimental scurvy combined with infection and rheumatic fever, Jr. Exper. Med., lix, 97–114.
4. RINEHART, J. F.: Does vitamin C deficiency play a rôle in rheumatoid arthritis? (Paper read before California Medical Association, May 1934.)
5. KLINGE, F.: Das Gewebsbild des fieberhaften Rheumatismus. XII. Mitteilung. Zusammenfassende kritische Betrachtung zur Frage der geweblichen Sonderstellung des rheumatischen Gewebschadens, Virchow's Arch. f. path. Anat., 1932, ccxxcvi, 344–388.
6. NICHOLS, E. H., and RICHARDSON, F. L.: Arthritis deformans, Jr. Med. Res., 1909, xvi, 149–221.
7. FISHER, A. G. T.: Chronic (non-tuberculous) arthritis, 1929, Macmillan Co., New York.
8. LLEWELLYN, L. J., and JONES, A. B.: Fibrositis, 1915, William Heinemann, London.
9. GOLDTHWAIT, J. E.: Infectious arthritis, Boston Med. and Surg. Jr., 1904, cl, 363–371.
10. SWAIM, L. T.: Arthritis, Pennsylvania Med. Jr., 1931, xxxiv, 535–537.
11. HOWITT, F. D., and CHRISTIE, W. F.: The malnutrition factor in rheumatoid arthritis, Lancet, 1931, 1282–1287.
12. JACKSON, L., and MOORE, J. J.: Studies on experimental scurvy in guinea pigs, Jr. Infect. Dis., 1916, xix, 478–514.
13. SMITH, E. A.: A study of the alimentary tract in experimental scurvy (guinea pig), Am. Jr. Physiol., 1927, lxxx, 288–300.
14. HOWE, P. R.: Food in relation to teeth, Jr. Dental Res., 1921, iii, 7–37.
15. STINER, O.: Rheumatische Erkrankungen im Tierversuch, Mitteilungen aus dem Gebiete der Lebensmitteluntersuchung und Hygiene, 1929, xx, 1–8.
16. RINEHART, J. F.: Studies relating vitamin C deficiency to rheumatic fever and rheumatoid arthritis. I. Rheumatic fever, ANN. INT. MED., 1935, ix, 586–599.
17. PEMBERTON, R., and OSGOOD, R. B.: The medical and orthopedic management of chronic arthritis, 1934, Macmillan Co., New York.
18. CECIL, R. L.: Rheumatoid arthritis, Jr. Am. Med. Assoc., 1933, c, 1220–1227.
19. OSGOOD, R. B.: Orthopedic aspects of chronic rheumatism or arthritis (including an outline of concept of the American Committee for the Control of Rheumatism concerning the disease commonly called chronic rheumatism or arthritis), Jr. Am. Med. Assoc., 1930, xcv, 992–995.
20. Report of the British Medical Association Committee: Causation and treatment of arthritis and allied conditions, Brit. Med. Jr., 1933, i, 1033–1052.
21. SWAIM, L. T.: Atrophic arthritis, Rhode Island Med. Jr., 1923, vi, 51–55.

22. GOLDTHWAIT, J. E.: Arthritis—general considerations, Am. Med., 1930, xxxvi, 589–592.
23. BURNETT, F. L., and OBER, F. R.: Arthritis, anabolic nutrition and health, Am. Jr. Med. Sci., 1934, clxxxviii, 93–109.
24. IRONS, E. E.: The treatment of chronic arthritis, Jr. Am. Med. Assoc., 1934, ciii, 1579–1583.
25. FLETCHER, A. A.: The nutritional factor in chronic arthritis, Jr. Lab. and Clin. Med., 1930, xv, 1140–1144.
26. PEMBERTON, R.: Some metabolic and nutritional aspects of chronic arthritis, Am. Jr. Digest. Dis. and Nutr., 1934, i, 438–441.
27. ROWLANDS, M. J.: Rheumatoid arthritis: is it a deficiency disease? Proc. Roy. Soc. Med., 1927, xx, 41–68.
28. HALL, F. C.: Treatment of arthritis, Am. Med., 1929, xxxv, 367–372.
29. FLETCHER, A. A., and GRAHAM, D.: The large bowel and chronic arthritis, Am. Jr. Med. Sci., 1930, clxxxix, 91–93.
30. Arthritis Committee, University of California Medical School. (Unpublished observations.)
31. PEMBERTON, R.: Work of American Committee for the Control of Rheumatism; present status of arthritis, Med. Jr. and Rec., 1933, cxxxviii, 359–363.

THE EFFECTS OF CHRONIC DISEASE OF THE LIVER ON THE COMPOSITION AND PHYSICOCHEMICAL PROPERTIES OF BLOOD: CHANGES IN THE SERUM PROTEINS; REDUCTION IN THE OXYGEN SATURATION OF THE ARTERIAL BLOOD *

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THERE are many problems in connection with chronic parenchymatous disease of the liver which have never been satisfactorily explained on an anatomic basis alone. For instance, it is difficult to understand why certain individuals with moderate or advanced degrees of nodular cirrhosis have minimal symptoms or none at all; cirrhosis is frequently discovered at operation or necropsy in cases in which there have not been any symptoms of it, and this has given rise to much discussion as to what compensatory processes are involved. While it is true that the liver possesses extraordinary powers of regeneration and a large functional reserve capacity, these facts do not fully explain the persistence of anatomic changes in the organ and the maintenance of normal or nearly normal health.

One also sees numerous examples of "toxic" or other types of cirrhosis, in which recovery takes place even after all of the signs and symptoms of late hepatic disease have developed.[13] In some of these individuals, as in the experimental animal, the liver apparently returns to a normal anatomic and physiologic state; in others, the liver retains the appearance of disease, but for all practical purposes it is functionally sound. The cirrhosis which is associated with splenic anemia is a case in point; it does not disappear after splenectomy, but the patient may be greatly improved in health by this procedure, and hepatic function may show only minor abnormalities when studied by means of appropriate tests.

These clinical observations, as well as numerous physiologic studies, lead one to believe that the liver is somehow concerned in the maintenance of the "internal environment" and that when under certain conditions it fails in this respect, a vicious circle is developed, leading to progressive disintegration of the hepatic parenchyma and further changes in the physiologic constants of the living organism. It is natural to search for such changes in the blood, since the liver is intimately connected with the production of certain of its constituents. The studies to be reported are concerned with the probable relation of the liver to the maintenance of the serum proteins and with the occurrence of changes in the oxygen content of arterial blood secondary to hepatic disease. It is apparent that changes in both of these physiologic constants have some bearing on the clinical

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manifestations of hepatic damage and that they may be in some manner related to the production of the "vicious circle" of progressive deterioration or destruction of the liver cells.

Serum Proteins in Hepatic Disease

The relation of the liver to the production of plasma proteins has been disputed; although it is generally agreed that fibrinogen is exclusively a hepatic product,[17] it is not certain that serum albumin and serum globulin are manufactured in the liver alone. Direct proof is not available at present, but experimental data furnish some indirect evidence implicating the liver in formation of these substances.

Kerr, Hurwitz and Whipple[27, 28, 29] in a series of papers (1918) reported that there was regeneration of the serum proteins following plasmapheresis and that the globulin was replaced more rapidly than the albumin. They noted that, after a 50 per cent depletion of serum proteins, regeneration took place in from five to seven days, which happened to be exactly the time required for regeneration of the liver cells after an episode of hepatic necrosis produced by carbon tetrachloride. It was also observed that phosphorus and carbon tetrachloride poisoning resulted in moderate decreases in the serum proteins, and that regeneration of the protein occurred slowly in the presence of hepatic injury or of an Eck fistula.

Sawada later observed a decrease in the albumin and an increase in the globulin content of the serum following experimental schistosomiasis, and in phosphorus, chloroform, and carbon tetrachloride poisoning, and Bollman has noted similar changes in experimental hepatic lesions produced by various substances. Fiessinger and Gothie have shown a decrease in the total protein content of the serum after hepatectomy and a decrease in the total protein, with reversal of the albumin-globulin ratio after the production of an Eck fistula. Recent work (1934) from Whipple's[25, 26] laboratory has given support to the theory that the liver is intimately concerned in the formation of serum proteins. These studies suggest that there is a reserve of protein-building material in the organism which is stored, at least in part, in the liver and which is probably at least 50 per cent albumin or albumin-producing material. Whipple and his coworkers also concluded that there is probably a dynamic equilibrium between tissue and plasma protein, in which equilibrium the stored material in the liver probably figures.

There is a long series of reports on the relation of hepatic disease to the level of serum protein, the first of which contained the observations of Gilbert and Chiray, and Grenet[1, 2, 7, 8, 18, 20, 39, 40, 41, 42, 54, 57, 64] (1907). It has been observed repeatedly that in advanced chronic hepatic disease, there is frequently a moderate reduction in the total amount of serum protein, the diminution occurring chiefly in the albumin fraction, with reversal of the albumin-globulin ratio. In the less advanced cases, the albumin may be

only moderately reduced and the globulin actually increased; infection probably is responsible for the latter finding.[52] In any type of hepatic disease, however, the effects on the albumin-globulin ratio are much the same. In advanced chronic hepatic disease, albumin-globulin ratios as low as 0.3 have been observed; in less serious types, the changes are not so marked or constant, and the ratio tends to return to normal as improvement takes place. The data in a small series of selected cases observed during the last year are presented graphically in figure 1. These results are in accord with the

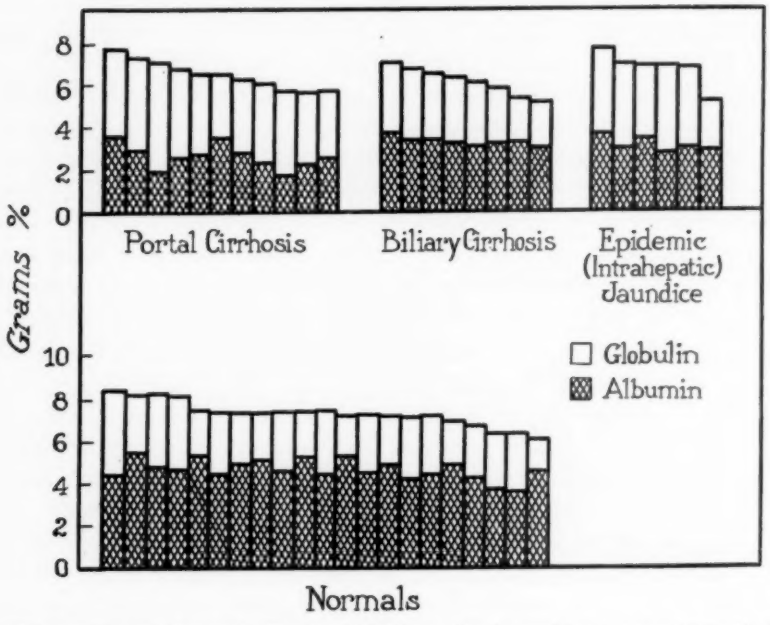

FIG. 1. The serum proteins and albumin-globulin ratios in various types of hepatic disease.

reports on clinical cases mentioned in the literature and also with those recently reported by Myers and Keefer.[39] In a fairly large series of cases of all types of hepatic disease I have found only a few in which the normal albumin-globulin ratio was not disturbed, although the total proteins were not necessarily reduced. The rapidity with which changes in the total protein and the albumin-globulin ratio may take place is rather striking, and repeated determinations on the same individual indicate that these changes may not be without some prognostic significance. Peters and Eisenman have properly raised the objection that these variations in the serum proteins may be of nutritional origin, rather than being attributable to failure of production of protein in the liver. However, the degree of malnutrition in many of the cases cited was not conspicuous, and the rapidity with which variations occur is not easily explained on a nutritional basis. It has also been noted that in hepatic disease, feeding of protein has little effect on

either the total serum protein or on the albumin-globulin ratio. The amount of protein lost in ascitic or edema fluid does not seem to be a factor; Barnett and his collaborators noted one patient who lost an average of 10 gm. of protein daily in the ascitic fluid over a long period of time and yet maintained the plasma proteins at a fairly constant although somewhat lowered level. In general, the clinical and experimental evidence related to lowered serum protein in cases of hepatic injury seems to indicate a failure of production of protein or protein-building substances on the part of the liver, with an altered equilibrium between circulating and stored protein. The fact that changes occur chiefly in the albumin fraction is in accord with the previously observed fact that it is formed less readily than globulin.[6, 32]

The principal effects referable to the reduced albumin content of blood serum of patients with hepatic disease are obviously related to the production of ascites and edema. The "edema level" (4 to 5 gm. per 100 c.c.) for the total serum proteins is not often reached, but the disproportionate reduction in serum albumin may reduce the osmotic pressure of blood serum sufficiently to produce transudation, especially in regions where venous stasis occurs. As Wells and his collaborators have shown by direct measurement, the specific osmotic pressure of serum is a linear function of its concentration of albumin; the globulin content is relatively unimportant. In malnutrition, edema may occur with values for serum albumin of less than 3 gm. per 100 c.c.[10]; in the serum of nine of 11 patients with ascitic cirrhosis (figure 1), the value for albumin was 3 per cent or less. In the cases of obstructive biliary cirrhosis, and in those of intrahepatic jaundice, the albumin was at or near the 3 per cent "edema level," but not more than 4 per cent in any case. These patients had neither ascites nor appreciable edema. It should be noted that ascites in hepatic disease does not necessarily depend on the level of serum albumin alone; since one encounters readings of 3.5 to 4 gm. per 100 c.c. in the presence of ascites, and lower figures in cases in which ascites is absent, such factors as portal venous stasis and chronic peritoneal irritation must also play an important part. The lowered serum albumin is a contributing factor only. Other effects of a lowered content of serum albumin on the organism are largely matters of conjecture; disturbances in general tissue nutrition may be produced by this means, but proof is lacking. One diagnostic procedure, the Takata-Ara reaction, may be dependent on variations in the content of serum protein, and especially on the relatively high values for globulin [23]; a small experience with this test indicates that there is possibly some correlation between positive tests and reversed albumin-globulin ratios.

One may conclude that one of the fairly constant effects of parenchymatous hepatic disease is reduction in the serum albumin and reversal of the albumin-globulin ratio; that these changes are most probably related to deficient production of protein by the liver, and that for this reason they may have some diagnostic and prognostic significance; and finally, that the serum albumin is often at or near a level which makes the production of ascites and edema relatively easy.

Reductions in the Oxygen Saturation of the Arterial Blood

My attention was first called to the possibility of anoxemia being a factor in hepatic disease by the work of Rich, who noted that in pernicious anemia there was atrophy of the cells around the central veins of the hepatic lobules, presumably the result of oxygen want. He showed subsequently that the same lesions were present after simple hemorrhage in experimental animals, and confirmed MacCallum's observations that this same type of atrophy was found in certain types of chronic passive congestion of the liver. Later Rich and Resnik showed that if animals were kept in an atmosphere low in oxygen, atrophy of the cells of the central portion of the lobule developed; Campbell and Rosin have made similar observations, and Loewy has noted certain physiologic and chemical changes in the liver under the same conditions. With these findings in mind, the possible relation of oxygen want to other chronic hepatic lesions was investigated.

Methods and Technical Considerations. Arterial blood for analysis was obtained by arterial puncture from the brachial artery under local anesthesia with procaine. Venous blood was drawn, without stasis, from the median or the basilic vein. A sterile syringe containing 5 c.c. of sterile mineral oil, free of air bubbles but not previously evacuated, was used in collecting each specimen. Immediately after withdrawal, the blood was placed under mineral oil in a small beaker, and a few crystals of potassium oxalate in the beaker were mixed with the blood by gentle stirring with a small glass rod. Analysis of these samples was made for oxygen and carbon dioxide content; most of the analyses were completed within an hour; all were completed within three hours after the blood was drawn. In a few cases the determinations were repeated four to six hours later. This delay resulted, in each instance, in only slight increase (1 to 2 per cent) in the oxygen content of the oil-protected sample. Samples of blood used for determination of oxygen capacity were equilibrated with room air and at room temperature by rotating in a 150 c.c. separatory funnel for 15 minutes or longer; constant rotation of the funnel insured maximal exposure of the blood. The technic and apparatus used in determining oxygen and carbon dioxide in arterial and venous bloods were essentially those described by Van Slyke and Neill in 1924, using a modified oxygen absorption mixture as introduced by Van Slyke in 1927. Determinations were done in duplicate, simultaneously, on two machines of the closed manometer type. "Percentage saturation," more correctly stated as "percentage oxygenation," was calculated by dividing the oxygen content by the oxygen capacity; both content and capacity were expressed in volumes of oxygen in 100 c.c. of blood.

Case Reports

Case 1. The first case studied was that of a man, aged 46 years, of pronounced alcoholic habits, who presented himself because of weakness, loss of weight, and jaundice of two months' duration. On examination the peculiar, dusky color of the

facies attracted attention; there seemed to be definite cyanosis in addition to visible jaundice. Examination of the lungs gave entirely negative results. The heart was slightly enlarged; the apex was felt just to the left of the nipple line. The pulse rate averaged about 100 beats per minute while the patient was at rest, and the patient was definitely dyspneic on slight exertion. The blood pressure, in millimeters of mercury, was 130 systolic and 90 diastolic. The liver was symmetrically enlarged and firm; the spleen could not be felt, and there was a small amount of free fluid in the abdomen. The urine was negative. There were 16 gm. of hemoglobin per 100 c.c. of blood, as measured by spectrophotometric methods, corresponding to an oxygen capacity of 21.4 volumes per cent. The erythrocytes numbered 3,780,000, and the leukocytes 9,400 per cubic millimeter of blood, and the differential formula was normal. Examination of stained blood smears disclosed slight macrocytosis. A serologic test for syphilis was negative. Roentgenologic and fluoroscopic examinations of the chest revealed nothing of importance, except slight, diffuse widening of the aortic shadow. The urea, uric acid, and sugar content of the blood serum were normal. The bilirubin content of the blood serum was 4.4 mg. per 100 c.c. The fragility of the erythrocytes was normal. The liver functional test with bromsulphalein disclosed retention of dye, grade 4. A galactose tolerance test revealed excretion of 3.36 gm. of reducing substance in five hours. There was definite oxygen unsaturation of the arterial blood, as is shown in table 1. Spectroscopic examination of the blood did not give evidence of methemoglobin or sulphemoglobin.

The patient was reëxamined two months later. The slight cyanosis and jaundice were unchanged, and the liver was definitely smaller, but the anemia had increased somewhat; the concentration of hemoglobin was 11.1 gm. per 100 c.c. of blood, corresponding to an oxygen capacity of 14.8 volumes per cent. The liver functional test with bromsulphalein gave evidence of retention of dye, grade 3. Careful reëxamination of the lungs and heart by physical, roentgenologic, and fluoroscopic means did not give evidence of any definite pulmonary or cardiac lesion.

At the last examination, four months later, the patient was definitely dyspneic and orthopneic, and both the cyanosis and ascites apparently had increased somewhat. Again, no pulmonary or cardiac lesion could be demonstrated to account for the anoxemia. Saturation of the arterial blood with oxygen was even lower than before, and saturation of the venous blood, which previously had been within normal limits, was significantly reduced. Retention of bromsulphalein, grade 2, persisted. After inhalation of 50 per cent oxygen for 10 minutes, the arterial saturation of oxygen was only 88 per cent. It seemed possible that the cyanosis was connected in some way with the probable hepatic cirrhosis, since there were no cardiac lesions or lesions of the respiratory tract to explain the condition.

The patient died suddenly one month later, from a profuse gastrointestinal hemorrhage. Roentgenologic examination of the stomach previously had been negative, and it was assumed that the source of the hemorrhage was esophageal varices.

Case 2. The second patient, an obese man, aged 49 years, presented a typical clinical picture of portal cirrhosis, probably of alcoholic origin. An adenomatous goiter with mild hyperthyroidism, and a basal metabolic rate 25 per cent above normal also was present, but there was no demonstrable cardiac incompetence at any time. The oxygen content of the arterial and venous blood was determined before and after thyroidectomy, and again several months later; the results are noted in table 1. To conserve space, further details of the clinical course are omitted. Because of the complicating factor of the hyperthyroid state and the possible effect on the circulation, these data may not be admissible as evidence.

Case 3. This patient, a man, aged 58 years, presented a somewhat different situation, in which extraneous factors were fairly well eliminated. He also had a definite history of alcoholism. He presented himself at the clinic because of jaundice

TABLE I

Repeated Determinations, with Particular Reference to the Administration of Oxygen, of Oxygen Content of the Blood of Three Patients Who Had Portal Cirrhosis

Date	Ascites, grade	Serum bilirubin, mg. per 100 c.c.	Bromsulphalein retention, grade	Oxygen, capacity volumes, per cent	Arterial oxygen		Venous oxygen		Remarks
					Content, volumes per cent	Saturation, per cent	Content, volumes per cent	Saturation, per cent	
Case 1									
3–28–33	1+	4.4	4	19.6	15.63	79.6	14.7	74.9	Portal cirrhosis; ascites; jaundice
5–21–33	1+	5.6	3	15.6	13.1	84.0	7.76	49.7	
9–12–33	2+	5.3	2	15.0	10.5	70.0	4.4	29.0	
						88.0			After 10 minutes in 50 per cent oxygen
Case 2									
2– 6–34	1+	5.6	3	20.26	16.43	81.0	12.77	63.0	Portal cirrhosis; mild hyperthyroidism
2–13–34		2.0	3	17.27	16.22	93.9	14.25	82.5	After 90 minutes in 60 per cent oxygen
2–28–34	0	3.6	3	14.9	13.6	91.2	11.4	76.5	After thyroidectomy
11–28–34	2+	3.4	3	19.3	17.0	88.0	8.9	46.0	Ascites and edema present
Case 3									
2– 9–34	3	4.4	4	14.67	12.3	83.8	5.7	38.8	Portal cirrhosis, ascites, jaundice on admission
									Before paracentesis
2–14–34	1	4.7		13.95	11.97	85.8	6.2	44.4	After paracentesis
2–20–34*		3.9		13.86					
2–22–34	1+	3.8		13.3	12.44	92.9	9.0	67.8	Patient in 50 per cent oxygen

* Carbon monoxide capacity of blood 14.0 volumes per cent; iron content 29.4 mg. per 100 c.c.

of five months' duration, and ascites and edema of two weeks' duration. Physical examination revealed a dropsical and jaundiced individual who was in poor general condition. The diaphragm was somewhat elevated, and a few inconstant, moist râles were heard at the bases of the lungs posteriorly. The abdomen was distended with fluid, and there was definite edema of the legs and genitalia. Examination of the heart revealed no objective findings of consequence. The systolic blood pressure, in millimeters of mercury, was 132, and the diastolic, 82. The pulse rate was 112 beats per minute. Visible collateral circulation was noted over the abdomen, and the liver was moderately enlarged. The patient was hospitalized immediately for further study.

Among the significant laboratory findings were definite macrocytic anemia; the value for hemoglobin was 10 gm. per 100 c.c., corresponding to an oxygen capacity of 13.4 volumes per cent, and erythrocytes numbered 3,170,000 per cubic millimeter of blood. The urea content of the whole blood was 22 mg., and the bilirubin content, 4.4 mg. per 100 c.c. Liver functional tests disclosed retention of bromsulphalein, grade 4. Electrocardiographic examination was negative. Roentgenologic examinations of the chest gave no evidence of appreciable increase in density at the bases of the lungs. The arterial oxygen saturation was reduced (table 1), and there was only slightly greater saturation after 4,000 c.c. of ascitic fluid had been withdrawn by paracentesis. There was, however, a slight rise in the oxygen saturation of the venous blood after this procedure. Following paracentesis, the cardiac output was 5.6 liters per minute (2.55 liters per minute per square meter of body surface). The blood was negative for methemoglobin and sulphemoglobin on spectroscopic examination. A few days after the second series of oxygen studies, a small area of congestion was made out in the base of the right lung, both by physical means and by roentgenologic examination. The patient was kept in an atmosphere containing 50 per cent oxygen for several days, in which time the chest cleared up entirely, and the arterial oxygen saturation rose to practically normal. Following a blood transfusion and another paracentesis, the patient was dismissed from the hospital considerably improved. He died, however, two months later in typical hepatic coma. Throughout his stay in the hospital the chest was examined daily for any lesion which might of itself tend to produce anoxemia, but with the exception of the small area of congestion previously referred to, there were never any findings of consequence. As has been noted, the original oxygen studies were made before and after paracentesis, while the chest was, for all practical clinical purposes, clear, although some edema of the alveolar walls could not, of course, be excluded.

Comment

With these three cases in mind, further study of the problem was begun, and determinations of oxygen were made on the arterial and venous blood of a series of patients who had portal cirrhosis; a group of controls was checked at the same time.

Of 20 persons studied, consisting of ambulant individuals of both sexes, chiefly healthy laboratory workers or patients who had peripheral vascular disease, the oxygen capacity of the blood ranged from 16.8 to 22.9 volumes per cent, with a mean of 19.6 volumes per cent. The arterial oxygen saturation varied from 90.8 to 98.4 per cent (average 94.7); the lowest reading was obtained on a patient who had thromboangiitis obliterans and extensive phlebitis; moreover, some antecedent pulmonary infarction could not be absolutely excluded. Thirteen hospital patients, chiefly patients with complicated or recurrent peptic ulcers, cholecystic disease, or gastric carcinoma

without evident metastasis, were also examined. In this group, the oxygen capacity ranged from 16.0 to 23.2 volumes per cent, with a mean value of 18.4 volumes per cent; the average arterial oxygen ranged from 92 to 95 per cent, with a mean value of 93 per cent. As might be expected, the average venous saturation was slightly lower in the ambulant group (64.7 per cent) than in individuals who were at more or less complete rest in bed (67.6 per cent). The figures relative to the ambulant patients are similar to those given by Peters and Van Slyke, and by Harrop, for normal subjects; the results on patients who were confined to bed were slightly lower, a fact which may be explained by their inactivity, weakness, and possibly by a sluggish pulmonary circulation.

Data on the oxygen capacity, content and percentage saturation of arterial and venous blood in a group of 20 additional patients who had portal cirrhosis are given in table 2. It should be noted that five patients of the group (cases 14 to 18 inclusive) displayed only minor degrees of arterial oxygen unsaturation; that three of these had syphilitic cirrhosis; and that one of this group of three (case 11) was definitely anemic and had no ascites at the time of examination. In this case, however, there was definite oxygen unsaturation of the arterial blood (12.2 per cent) on light exercise. Another of this group of three (case 16) had had ascites intermittently for three years, but had remained in good general condition. The third (case 19) had had a recent profuse gastrointestinal hemorrhage and at the time of examination was very anemic. Of the remaining 15 patients, two (cases 4 and 5) demonstrated arterial oxygen unsaturation of more than 15 per cent, and both were in very poor condition, death occurring within a few weeks after the examination in question. Somewhat more than half of the whole group had a percentage oxygenation (85 to 90 per cent) of arterial blood, corresponding to that which is found in normal persons living at high altitudes. Jaundice apparently was not essential for the presence of anoxemia; the amount of ascitic fluid and the degree of abdominal distention in the group also varied considerably, without apparent effect on the degree of oxygen unsaturation of arterial blood. The actual percentage of hemoglobin present, and consequently the oxygen capacity, did not appear to be a factor, although the arterial blood of the most anemic patient in the group was of approximately normal oxygen saturation. With improvement in the patient's condition (two cases), normal values for oxygen saturation were obtained. The acuteness of the hepatotoxic process, its severity, and the general condition of the patient seemed to be paralleled roughly by the percentage oxygen saturation of the blood in any given case.

In portal cirrhosis, there remains some probability that in certain cases the anoxemia is related to the ascites, to the subsequent elevation of the diaphragm and atelectasis of the lungs, and also, possibly, to clinically unrecognizable edema of the alveolar walls. However, certain patients represented in table 1 had definite ascites, and yet the arterial oxygen unsaturation in these cases fell within the range of the ambulatory control group; the

TABLE II

Blood Oxygen Content of Patients Who Had Portal Cirrhosis

Case	Oxygen capacity, volumes per cent	Arterial oxygen		Venous oxygen		Serum bilirubin, mg. per 100 c.c.	Bromsulphalein retention	Remarks
		Content, volumes per cent	Saturation, per cent	Content, volumes per cent	Saturation, per cent			
4	28.2	21.2	77.4	20.8	13.7	4.0	2	Polycythemia vera; hepatitis with portal thrombosis; hepatic and renal insufficiency (verified at necropsy)
5	13.1	10.74	82.6	9.35	71.9	12.5	.....	Alcoholic cirrhosis; ascites; jaundice; poor condition
6	11.4	9.92	87.0	5.84	51.2	1.0	2	Cirrhosis; ascites (surgically verified)
7	15.0	13.1	87.3	11.1	74.0	3.8	3	Alcoholic cirrhosis; ascites; jaundice
8	15.3	13.7	87.3	10.3	67.3	1.4	3	Alcoholic cirrhosis; ascites
9	16.4	14.5	88.1	13.85	84.4	9.4	3	Alcoholic cirrhosis; ascites, grade 1, slight jaundice
10	18.3	16.15	88.4	12.45	68.1	1.3	2	Alcoholic cirrhosis with ascites (surgically verified); figures verified on two subsequent days
11	18.6	16.6	89.2	10.8	58.0	5.8	4	Alcoholic cirrhosis; ascites
12	20.5	18.27	89.2	8.13	39.6	8.0	.....	Alcoholic cirrhosis; ascites; jaundice
13	17.7	16.0	90.3	12.2	68.9	4.4	4	"Compensated" cirrhosis (alcoholic)
14	11.8	10.9	92.3	3.3	28.0	1.0	2	"Compensated" cirrhosis (syphilitic); arterial saturation 87.8 per cent after light exercise
15	13.2	12.2	92.4	8.7	63.9	11.0	.....	Portal cirrhosis (verified at necropsy, after death from mesenteric thrombosis)
16	16.5	15.6	92.7	14.5	87.8	2.0	2	Syphilitic hepatitis; ascites of three years' duration
17	21.9	20.4	93.1	.....	.....	1.5	2	Portal cirrhosis; etiology unknown
18	4.23	3.97	93.8	0.9	21.0	1.0	4	Syphilitic cirrhosis; recent hemorrhage
19	11.4	9.4	82.4	7.2	65.9	9.1	4	Toxic cirrhosis with ascites; jaundice; hepatic insufficiency
	14.8	13.3	89.8	12.4	63.1	10.0	.....	After paracentesis and transfusion
20	14.15	12.3	86.9	5.88	41.9	1.0	3	Banti's disease (surgically verified); portal cirrhosis
	12.15	11.96	96.0	.....	.....	.....	.....	One year later; much improved; toxic cirrhosis
21	19.6	17.3	88.3	11.8	60.2	15.0	.....	Ascites; jaundice; small pleural effusion
22	19.3	16.7	86.5	.....	.....	1.5	2	Ascites; portal cirrhosis; surgically verified. In O_2 arterial oxygenation 96 per cent
23	24.68	21.75	88.1	17.07	69.5	1.0	4	Polycythemia vera; portal cirrhosis
	23.7	22.0	92.8	20.0	84.3	1.0	3	One year later; marked symptomatic improvement

principal factor which these patients had in common was that the condition was chronic, and the general condition of all these individuals was reasonably good. The sudden death of one patient in the group, from mesenteric thrombosis, allowed for verification of the hepatic lesion at necropsy; a definite nodular type of cirrhosis was found. An opportunity also presented itself, at this time, to study the purely mechanical effect of ascites on two other patients, one a man, aged 50 years, who had active tuberculous peri-

tonitis and a normal liver, verified both by appropriate functional tests and at operation, and the other was a woman, aged 40 years, who had chronic glomerulonephritis, ascites, and edema; in both cases, the arterial oxygen unsaturation was not appreciably greater than that noted in other cases in which patients were bedfast; the percentage saturation of the arterial blood in the first case was 91.3 per cent, and in the second, 93.2 per cent.

In order to distinguish further between the possible mechanical factors involved and the effect of the hepatic disease per se, a second and third group of cases were studied, including patients who had various types of acute parenchymatous hepatic damage and also patients who had prolonged obstructive jaundice, attributable to stricture of the common duct, neoplasm, and stone. In only one case of this group was ascites present. The results are given in tables 3 and 4. It will be noted that in three of the six cases in which jaundice of the "intrahepatic" type was present (table 3), mod-

TABLE III

Blood Oxygen Content of Patients Who Had Intrahepatic Jaundice

Case	Serum bilirubin, mg. per 100 c.c.*	Oxygen capacity, volumes per cent	Arterial oxygen		Venous oxygen		Remarks
			Content, volumes per cent	Saturation, per cent	Content, volumes per cent	Saturation, per cent	
24	12	15.8	14.6	92.4	Not obtained		"Toxic" jaundice of unknown origin
25	30	16.5	15.2	92.1	11.3	68.4	Infectious (epidemic) jaundice
26	20	18.0	16.4	91.0	8.0	44.4	Epidemic jaundice
27	15	18.3	16.3	89.0	9.7	53.0	"Toxic" jaundice of unknown origin
28	7	18.0	16.5	87.3	8.4	44.4	"Toxic" jaundice of unknown origin
29	15	19.3	16.8	86.0	9.0	46.6	Chronic hepatitis (cinchophen)

* Highest recorded level in each instance.

erate degrees of unsaturation of the arterial hemoglobin were observed; the most marked change was noted in a case of severe hepatitis attributable to cinchophen.

In the nine cases of obstructive jaundice and various degrees of hepatitis, cholangitis, and biliary cirrhosis (table 4), the blood of only one patient was of normal oxygen saturation; the blood of five other patients gave values which averaged about 5 per cent below normal, and in the remaining three, strikingly low values were obtained. Two of these patients had stricture of the common duct of long duration, with extreme degrees of obstructive biliary cirrhosis; a third patient (case 37) had very marked cholecystitis, hepatitis, and cholangitis, and was deeply jaundiced at the time of examination; in this case, the normal figures obtained one month

TABLE IV

Blood Oxygen Content of Patients Who Had Obstructive Jaundice

Case	Serum bilirubin, mg. per 100 c.c.*	Oxygen capacity, volumes per cent	Arterial oxygen		Venous oxygen		Remarks
			Content, volumes per cent	Saturation, per cent	Content, volumes per cent	Saturation, per cent	
30	18	12.17	11.57	95.0	9.2	75.5	Stricture of common duct; good general condition
31	4	17.2	15.8	91.8	11.5	66.8	Stone in common duct, biliary cirrhosis, jaundice, slight ascites
32	15	16.7	15.2	90.8	12.1	72.4	Carcinoma of pancreas with obstructive jaundice
33	11	19.6	17.5	89.5	8.3	42.3	Stone in common duct; biliary cirrhosis
34	9	9.67	8.6	88.9	3.07	31.7	Stricture of common duct of long duration; marked biliary cirrhosis with hemorrhagic tendency
35	32	9.2	7.6	82.6	6.1	31.7	Stricture of common duct and hepatic insufficiency; extremely ill
36	22	16.5	13.18	79.8	12.5	75.7	Marked biliary cirrhosis; carcinoma of gall-bladder with metastasis; portal thrombosis
37	34	2/6					
		18.5	15.3	82.7	5.8	31.4	Severe cholangitis and hepatitis before operation
		3/12					
		17.95	17.5	95.2	.....	.....	After operation; much improved
38	14	17.2	15.5	90.1	8.5	49.5	Carcinoma of pancreas and cirrhosis, grade 3
		20.7	17.5	80.4	.....	.....	Coma hepaticum (two weeks later)

* Highest recorded level in each instance.

after operation coincided with the striking clinical improvement which had occurred in the interval. In one other case (case 33), a postoperative determination of the arterial and venous oxygen content was made, but little change was noted from the earlier figure; this was to be expected in view of the advanced hepatic fibrosis and biliary cirrhosis, which followed six months of obstructive jaundice caused by stone in the common duct. Case 38 was of special interest because of the low percentage oxygenation of the arterial blood noted while the patient was in hepatic coma, a point which will be mentioned later.

In the whole group of patients who had hepatic disease, the degree of oxygen unsaturation of the arterial blood seemed to reflect the general condition of the patient; numerous exceptions were noted, but in general a normal or slightly reduced oxygen saturation of the arterial blood was found only when the patient's general condition was better than the average; a very low figure for oxygen saturation usually indicated a condition bordering on hepatic insufficiency. These observations on clinical subjects are supported to a very considerable extent by studies on experimental animals, the details of which will be reported subsequently by Bollman and me.

The possible causes of anoxemia in these cases require some discussion. There are, according to Peters and Van Slyke, four types of anoxia (anoxemia): (1) anoxic anoxia, a condition produced by high altitudes, chronic pulmonary or bronchial lesions, and congenital cardiac anomalies which allow for admixture of arterial and venous blood; (2) anemic anoxia, attributable to a decrease in the concentration of hemoglobin in the circulating blood; this may be attributable to anemia from various causes, or to the presence of inactive compounds of hemoglobin; (3) stagnant anoxia, attributable to failing circulation; this may be present in such conditions as cardiac failure and venous obstruction; (4) histotoxic anoxia, attributable to conditions in which the tissue cells are unable to take up oxygen from the circulating blood, as in poisoning with cyanides and alcohol. In the first type, anoxic anoxemia, there is a reduced percentage oxygenation of arterial blood; in the second, anemic anoxia, the percentage saturation of hemoglobin in arterial blood is normal, but the low content of functioning hemoglobin produces a low arterial and venous oxygen tension. In stagnant anoxia, the hemoglobin is normal in amount and the percentage oxygen saturation of the arterial blood is within normal limits, but the oxygen tension of the venous blood is low; in histotoxic anoxia, the arterial and venous hemoglobin are normally saturated with oxygen.

The results of the studies reported above, on oxygen content of the blood of patients with hepatic disease, indicate that the anoxemia is of the anoxic variety and that the cause may be tentatively assigned to some change in the lung or to a failing circulation. However, the latter could hardly be an important factor, especially if patients do not have ascites and edema. In dropsical patients it is not so easily excluded; however, in three such cases the cardiac output was normal or elevated, and in none of our cases was there any evidence of preëxisting cardiac disease. The arterial blood pressures in the whole group of cases studied were within the limits of normal. Attention is drawn to the lungs chiefly because of the observed increases in the oxygen saturation of arterial blood after inhalation of oxygen. As Lundsgaard and Van Slyke have noted, the fact that one can relieve visible cyanosis and increase the percentage saturation of arterial blood to normal levels by this means is fairly good evidence that the seat of the anoxemia lies in deficient absorption of oxygen from the alveoli. There were no constant or characteristic pulmonary findings in these cases; even on repeated physical and roentgenologic examination nothing of consequence could be made out in the chest except in the occasional case. The factor of shallow respiration, suggested by Meakins, may play a part, but it hardly seems sufficient to explain the whole picture. Vital capacity was somewhat reduced in certain of our cases, but this might be expected in any disease process of equal severity. Data obtained at necropsy, as one might expect, show some evidence of pulmonary lesions; in a series of 40 consecutive fatal cases of chronic parenchymatous hepatic disease, which Foley has reviewed, in about 80 per cent there was edema of the pulmonary bases, grade 1 or 2,

and terminal bronchopneumonia or hydrothorax, singly or in combination. On the basis of pathologic evidence, the pulmonary lesions were considered to be essentially terminal phenomena, and there was little to indicate that they played a part in the production of anoxic anoxemia during life. Edema of the alveolar walls, of minor degree, may cause reduction in arterial oxygen saturation, as Rühl has shown by the production of histamine shock in experimental animals; similar changes cannot be absolutely excluded in hepatic disease, and may constitute a major factor in the production of anoxemia.

Is it possible that changes in the hemoglobin itself could produce anoxemia of this type? There are adequate reasons to assume that the liver is concerned with formation of hemoglobin. The work of Whipple [63] and his collaborators indicates that "the liver participates in active fashion in the preparation of parent substances for hemoglobin production" and that in severe hepatic injury, with anemia, these hemoglobin-production factors can be shown by biologic assay to be greatly reduced. Similar low hemoglobin-production values have been demonstrated in cirrhosis by this same means,[50] especially if hepatic insufficiency had been present before death. This is in accord with the observed macrocytic anemia of chronic hepatic disease, the presence of which has been repeatedly noted and recently reviewed by Fellinger and Klima. Although the failure of hemoglobin-production under these conditions is evident, it is pure hypothesis to assume that the hemoglobin may be altered in a qualitative fashion, since it is generally supposed that hemoglobin of man is a substance of constant composition,[5, 11] and that its structure is not altered in disease. Such well known forms of inert hemoglobin as methemoglobin, sulphemoglobin, or carbon monoxide hemoglobin do not enter into consideration, since they can be demonstrated by spectroscopic examination, and in the cases studied the spectroscopic appearance of the blood was normal. The close correspondence between the values for hemoglobin and the figures for oxygen capacity of the blood in these cases eliminates, for practical purposes, the possibility of the formation of nitrobenzol hemoglobin or related compounds.[33] Other forms of inactive hemoglobin are largely hypothetical and can be excluded from consideration by the same means. However, Ray, Ray and Stimson, Stimson, and Stimson and Hrubetz in a series of papers, have discussed the question of a non-oxygen carrying hemoglobin which appears in the blood of rabbits after splenectomy. They also noted that after partial hepatectomy of rabbits, there was a discrepancy between the total pigment of blood and its ability to transport oxygen, and they called attention to a change in the spectroscopic appearance of blood under these conditions.

There remains, finally, the possibility that in hepatic disease the hemoglobin does not function normally as a respiratory pigment. For practical purposes, only two methods of study of the nature of hemoglobin are available, spectroscopic examination and examination of the dissociation curve of oxyhemoglobin in the specimen of blood in question. The former

method having failed to identify any known abnormal forms, Adams and I have attempted to utilize the latter method in the hope of identifying some variation in the type of hemoglobin produced by the diseased liver. It is known that the dissociation curves of hemoglobin are different in different species, and that there are also different temperature coefficients for oxygen exchange in different species.[36] Species variations in the specific ability of a particular hemoglobin to combine with various mixtures of carbon monoxide and oxygen are also recognized.[4, 5] These variations are thought to be attributable to alterations in the globin fraction; this component of the molecule probably is specific for any given species.

The form of the dissociation curve of normal oxyhemoglobin, under standard conditions, has been established by Barcroft; the blood of normal individuals which have been studied, using methods of double equilibration

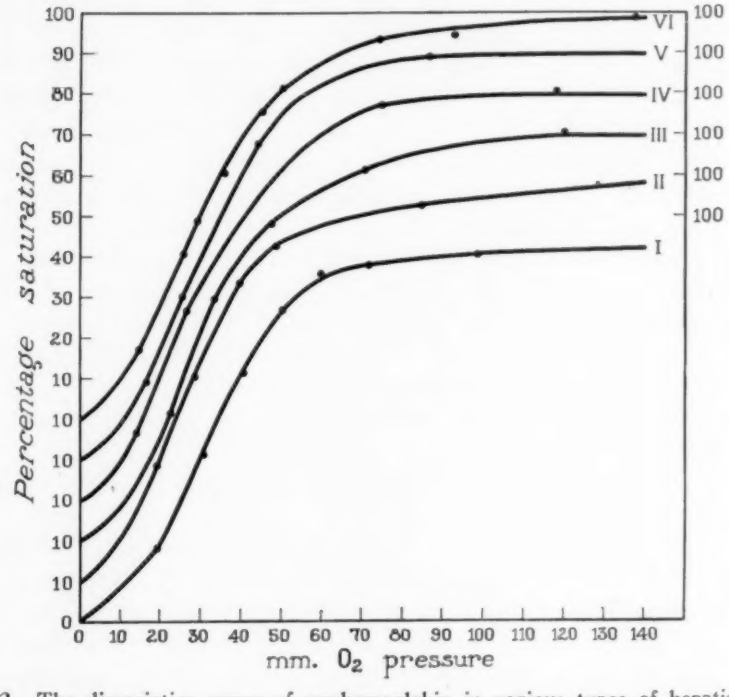

FIG. 2. The dissociation curve of oxyhemoglobin in various types of hepatic disease: (I) syphilitic cirrhosis, anemia; (II) portal cirrhosis; (III) portal cirrhosis, polycythemia; (IV) cholangitis, hepatitis; (V) splenic anemia, portal cirrhosis; (VI) normal.

similar to those described by Austin and his collaborators, shows a dissociation curve which falls along that drawn by him. The dissociation curves of blood taken from patients who have advanced hepatic disease will be described in more detail in a subsequent report; it suffices to say that the curves which have been obtained on specimens examined to date show little change from Barcroft's normal (figure 2). This is almost certainly true for bloods which contain little or no excess of bilirubin; in the blood of

jaundiced individuals and experimental animals some minor changes are noted. In blood from both jaundiced and non-jaundiced patients and animals, however, no changes have been so far observed in the dissociation curve of oxyhemoglobin which have a direct bearing on the degree and type of anoxemia under discussion. Whether the blood of a patient who has hepatic disease is definitely polycythemic, or very anemic and diluted, as it may be after hemorrhage, the dissociation curve is the same, although the amount of oxygen which is given off at any given oxygen tension may vary greatly because of the great discrepancy in the total content of hemoglobin (figure 3). Richards and Strauss have previously noted that the dissociation curves of anemic and polycythemic blood are similar. Under standard conditions in the very anemic patient, however, the element of anemic anoxia is important, as figure 3 shows. The behavior of the dissociation curve of oxyhemoglobin of patients who have hepatic disease must, of course, be studied at different carbon dioxide tensions before the strict normality of the hemoglobin in these cases can be established. Such studies are in progress at present. It should be noted, parenthetically, that the carbon dioxide content of both arterial and venous blood was determined in a number of cases in this series, and reductions which were in general agreement with the degree of anoxemia were obtained.

There are other possible alterations in the physical character of the blood in hepatic disease which may have a bearing on the rate of oxygenation in the lung. Alterations in concentration of the blood and in surface tension, such as are known to occur in jaundiced blood, blood concentration,[46] and variations in the permeability of erythrocytes to oxygen may be important in affecting the rate of passage of oxygen from the alveoli of the lung to the hemoglobin within the erythrocytes. All laboratory workers are familiar with the altered physical character of blood in hepatic disease, particularly if jaundice is present, and these changes, although neither measurable nor understood, may be important in the solution of the problem.

The following possible explanations for the anoxemia noted in hepatic disease are still under investigation: (1) that there are changes in the physical character of the blood which retard the rate of its oxygenation in the lung; (2) that there are hypothetical changes in the physiologic behavior of hemoglobin which can be shown only by a consideration of the time required for its complete oxygenation; (3) that the behavior of the pulmonary alveoli as a site for oxygenation is altered in some manner, possibly by changes in the alveolar wall, with resultant difficulty in diffusion of oxygen (Brauer's pneumoniosis) [35]; and finally, (4) that the engorged or contracted liver, with its mechanically altered blood flow, may decrease the rate of filling of the right auricle and indirectly reduce the rate of blood flow through the pulmonary capillaries, thus reducing the speed at which blood can be oxygenated. As Marie Krogh has noted, a reduced pulmonary blood flow results in a slow moving layer of blood along the capillary wall, with a more rapidly moving

axial stream; under such circumstances, it is not difficult to see how the rate of diffusion of oxygen into blood might be reduced.

Whatever the explanation of this anoxemia may be, it seems likely that it may have some definite effect on the observed symptomatology of hepatic disease and on the progress of the hepatic lesion itself. The hepatic facies, with its characteristic muddy, subicteric hue, may owe at least a part of its

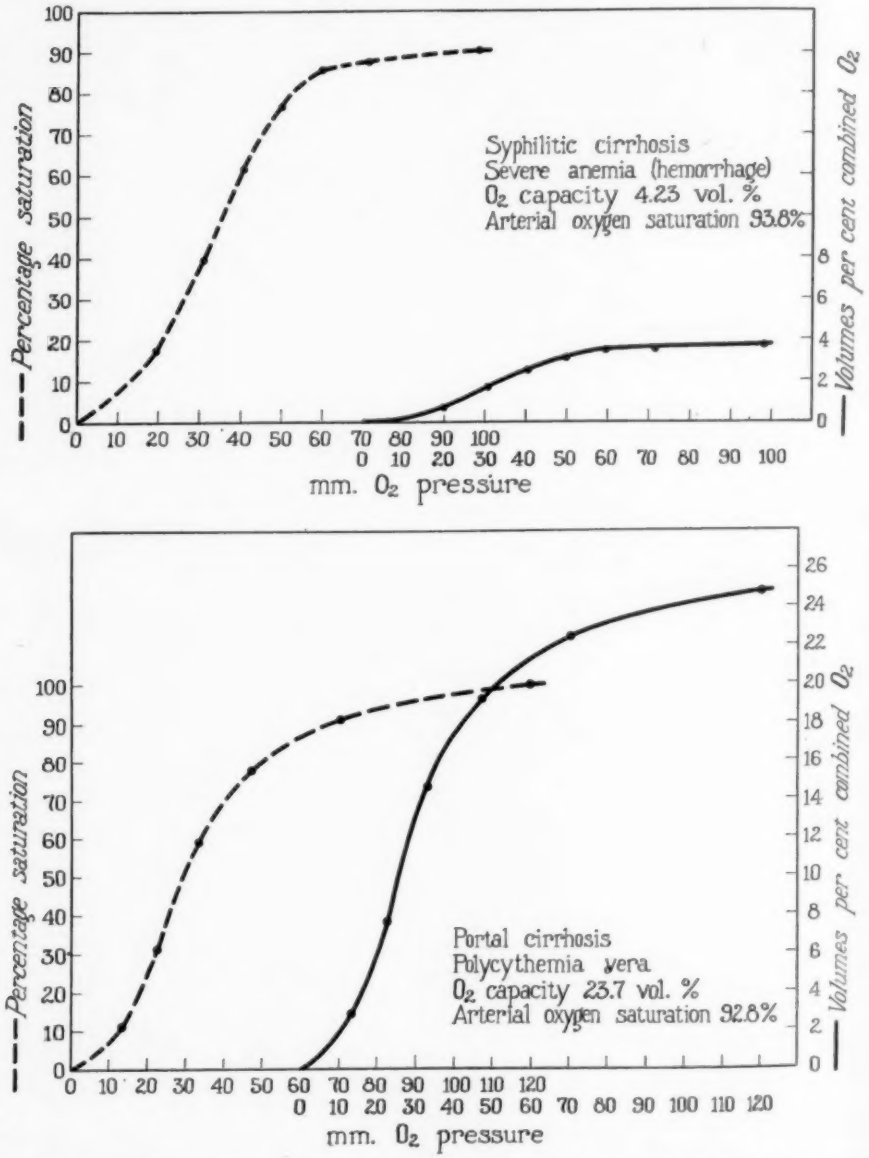

FIG. 3. The dissociation curve of oxyhemoglobin and the relative amounts of oxygen in combination at various oxygen tensions; two patients are represented. *Above*, anemia was present; *below*, polycythemia.

familiar color to the presence of considerable quantities of reduced hemoglobin in the capillary blood. Barcroft's description of the Cholos on Cerro de Pasco could be used almost verbatim in describing the appearance of a patient with chronic hepatic disease. The clubbed fingers, which are a feature of juvenile cirrhosis, and which may occasionally be observed in adults who have cirrhosis, are probably attributable to a decreased supply of oxygen to peripheral tissues. Lassitude, fatigue, and insomnia, similar to that seen in mountain sickness, are common in hepatic disease, and it is possible that in both conditions the basis for these symptoms may be the same. The respiratory and cardiac symptoms noted at high altitudes (palpitation, dyspnea, periodic breathing), as well as the gastrointestinal symptoms (nausea, vomiting, anorexia), also have been observed in association with cirrhosis. The accumulation of lactic acid in the blood, which was recently commented on by Roth and me, may well be a sequel of deficient tissue oxygenation, and the lactic acidemia of hepatic disease may be quite comparable to that observed at high altitudes. Finally, the symptoms of hepatic coma which are referable to the central nervous system may be caused in part, or at least aggravated, by the anoxemia.[24] Hitzenberger has made a similar suggestion in regard to the psychic changes of congestive heart failure. Stupor or coma, convulsions, the so-called pyramidal tract syndromes and the host of neurologic signs which may be encountered in hepatic insufficiency are not greatly different from those which have been observed with unmixed anoxemic states. In one case, in which the patient was in profound hepatic coma, a 20 per cent oxygen unsaturation was noted in the arterial blood, although a previous examination of this same individual had shown a figure not greatly reduced from the normal.

The probable effect of the reduced arterial oxygen saturation on the liver itself is obviously of considerable importance, since under conditions of anoxemia, either anoxic or anemic, definite atrophy of the central portion of the hepatic lobule takes place. The protective effect of oxygen against hepatotoxic substance, as shown by Goldschmidt, Ravdin, and Lucké, and the low tolerance of the experimental animal to carbon tetrachloride in the presence of low oxygen tensions [9] are more pertinent observations, so far as the clinical subject is concerned. It seems likely that the factor of anoxemia may hasten the deterioration of the hepatic parenchyma in some cases, the low oxygen tension of the hepatic arterial blood producing further atrophy of hepatic cells, and also rendering the parenchyma subject to toxic influences which ordinarily could be withstood without difficulty.

The anoxemia may also contribute its share to the production of ascites and edema; as Landis showed by direct observations on the mesentery of the frog, lack of oxygen increased the rate of filtration fourfold, and allowed the passage of proteins through the capillary wall. The anoxemia may also add to the difficulty of maintaining a normal circulation; hearts dilate at high altitudes, and artificial cardiac dilatation may be induced in experimental animals by lack of oxygen. Possibly the phenomenon of "decompensa-

tion " in hepatic disease may be related to circulatory weakness, together with an increased rate of filtration of fluid through capillary walls.

Finally, the question of compensatory mechanisms for this anoxemia must be considered. In certain of these cases, as in normal persons at high altitudes, there is a fall in the bicarbonate content of blood, an increase in cardiac output, and an accelerated respiration; the erythrocytosis which is so important a part of acclimatization to high altitudes does not appear, in spite of the stimulus of anoxemia, probably because of the failure of production of hemoglobin-building factors, except in the rather rare instances in which polycythemia and cirrhosis [22] occur jointly in the same individual.

Summary

It may be said that there are no constant demonstrable changes in the lung or circulation which explain the anoxemia observed in cases of advanced hepatic disease, although minor degrees of edema of the alveolar walls cannot be excluded; that such mechanical factors as ascites and abdominal distention are not necessary for its production; and that to date it has been impossible to demonstrate any variations in the physiologic behavior of hemoglobin sufficient to explain the difficulty with which the blood of these patients takes up oxygen. So far as the effect of anoxemia on the symptoms and course of the disease is concerned, it suffices to say that anoxemia, if of considerable degree and duration, can have only one effect and that this would be an unfavorable one. It would also appear that the patient who has a chronic hepatic lesion is poorly equipped to adjust himself to even the less severe degrees of anoxemia because of the limitation in production of hemoglobin. Although the evidence is admittedly incomplete, there is much to suggest that anoxemia is at least one of the factors on which a vicious circle of progressive disintegration of the hepatic parenchyma is established.

BIBLIOGRAPHY

1. Abrami, P., and Robert-Wallich: Modifications du sérum sanguin au cours des cirrhoses du foie avec ascite. Inversion du rapport sérines-globulines, Compt.-rend. Soc. de biol., 1929, ci, 291–293.
2. Atchley, D. W., Loeb, R. F., Benedict, E. M., and Palmer, W. W.: Physical and chemical studies of human blood serum. III. A study of miscellaneous disease conditions, Arch. Int. Med., 1923, xxxi, 616–621.
3. Austin, J. H., Cullen, G. E., Hastings, A. B., McLean, F. C., Peters, J. P., and Van Slyke, D. D.: Studies of gas and electrolyte equilibria in blood. I. Technique for collection and analysis of blood, and for its saturation with gas mixtures of known composition, Jr. Biol. Chem., 1922, liv, 121–147.
4. Barcroft, J.: The respiratory function of the blood. Part I. Lessons from high altitudes, 1925, Cambridge University Press, 200 pp.
5. Barcroft, J.: The respiratory function of the blood. Part II. Hemoglobin, 1928, Cambridge University Press, 200 pp.
6. Barker, M. H., and Kirk, E. J.: Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch. Int. Med., 1930, xlv, 319–346.

7. Barnett, C. W., Jones, R. B., and Cohn, R. B.: The maintenance of a normal plasma protein concentration in spite of repeated protein loss by bleeding, Jr. Exper. Med., 1932, lv, 683–693.
8. Bennett, T. I., Dodds, E. C., and Robertson, J. D.: A study of plasma-protein loss with edema but without proteinuria and its bearing on the concept of nephrosis, Lancet, 1930, ii, 1006–1008.
9. Bollman, J. L.: Studies on the experimental production of ascites. (Unpublished data.)
10. Bruckman, F. S., and Peters, J. P.: The plasma proteins in relation to blood hydration. V. Serum proteins and malnutritional or cachectic edema, Jr. Clin. Invest., 1930, viii, 591–595.
11. Butterfield, E. E.: Über die Lichtextinktion, das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und Krankhaften Zuständen, Ztschr. f. phys. Chem., 1909, lxii, 173–225.
12. Campbell, J. A.: Concerning the problem of Mount Everest, Lancet, 1928, ii, 84–86.
13. Chabrol, E., and Collet, J.: La curabilité de l'ascite dans les cirrhoses atrophiques du foie, Bull. et mem. Soc. méd. d. hôp. de Par., 1934, iii, 700–701.
14. Fellinger, K., and Klima, R.: Lebercirrhose und Anämen, Ztschr. f. klin. Med., 1934, cxxvi, 547–567.
15. Fiessinger, N., and Gothie, S.: L'évolution de l'équilibre albumine-globuline du sérum après l'hépatectomie totale et le fistula d'Eck chez le chien, Compt.-rend. Soc. de biol., 1933, cxii, 1053–1055.
16. Foley, M. P.: Unpublished data.
17. Foster, D. P., and Whipple, G. H.: Blood fibrin studies. IV. Fibrin values influenced by cell injury, inflammation, intoxication, liver injury, and the Eck fistula. Notes concerning the origin of fibrinogen in the body, Am. Jr. Physiol., 1922, lviii, 407–431.
18. Gilbert, A., and Chiray, M.: Diminution des substances albumineuses du sérum sanguin chez les cirrhotiques ascitiques, Compt.-rend. Soc. de biol., 1907, lxiii, 487–488.
19. Goldschmidt, S., Ravdin, I. S., and Lucké, B.: The effect of oxygen in prevention of hepatic necrosis produced by volatile anesthetics, Arch. Path., 1934, xviii, 593–594.
20. Grenet, H.: Diminution des albumines du sérum sanguin chez les hepatiques, Compt.-rend. Soc. de biol., 1907, lxiii, 552–553.
21. Harrop, G. A., Jr.: The oxygen and carbon dioxide content of arterial and of venous blood in normal individuals and in patients with anemia and heart disease, Jr. Exper. Med., 1919, xxx, 241–257.
22. Harrop, G. A., Jr.: Polycythemia, Medicine, 1928, vii, 291–344.
23. Heath, C. W., and King, E. F.: The Takata-Ara test in the diagnosis of liver disease, New Eng. Jr. Med., 1934, ccxi, 1077–1081.
24. Hitzenberger, K.: Über Störungen des Bewusstseins bei Kreislaufkranken infolge Sauerstoffmangels, Wien. klin. Wchnschr., 1933, xlvi, 865–869.
25. Holman, R. L., Mahoney, E. B., and Whipple, G. H.: Blood plasma protein regeneration controlled by diet. I. Liver and casein as potent diet factors, Jr. Exper. Med., 1934, lix, 251–267.
26. Holman, R. L., Mahoney, E. B., and Whipple, G. H.: Blood plasma protein given by vein utilized in body metabolism. II. A dynamic equilibrium between plasma and tissue proteins, Jr. Exper. Med., 1934, lix, 269–282.
27. Kerr, W. J., Hurwitz, S. H., and Whipple, G. H.: Regeneration of blood serum proteins. I. Influence of fasting upon curve of protein regeneration following plasma depletion, Am. Jr. Physiol., 1918, xlvii, 356–369.
28. Kerr, W. J., Hurwitz, S. H., and Whipple, G. H.: Regeneration of blood serum proteins. II. Influence of diet upon curve of protein regeneration following plasma depletion, Am. Jr. Physiol., 1918, xlvii, 370–378.
29. Kerr, W. J., Hurwitz, S. H., and Whipple, G. H.: Regeneration of blood serum proteins. III. Liver injury alone: liver injury and plasma depletion: the Eck fistula combined with plasma depletion, Am. Jr. Physiol., 1918, xlvii, 379–392.

30. KROGH, M.: The diffusion of gases through the lungs of man, Jr. Physiol., 1915, xlix, 271–300.
31. LANDIS, E. M.: Micro-injection studies of capillary permeability. III. The effect of lack of oxygen on the permeability of the capillary wall to fluid and to the plasma proteins, Am. Jr. Physiol., 1928, lxxxiii, 528–542.
32. LINDER, G. C., LUNDSGAARD, C., and VAN SLYKE, D. D.: The concentration of the plasma proteins in nephritis, Jr. Exper. Med., 1924, xxxix, 887–920.
33. LOEB, R. F., BOCK, A. V., and FITZ, R.: Acute nitrobenzol poisoning with studies on the blood in two cases, Am. Jr. Med. Sci., 1921, clxi, 539–546.
34. LOEWY, A.: Über das Verhalten der Leber unter Luftverdünnung, Biochem. Ztschr., 1927, clxxxv, 287–319.
35. LUNDSGAARD, C., and VAN SLYKE, D. D.: Cyanosis, Medicine, 1923, ii, 1–76.
36. MACĚLA, I., and SELIŠKAR, A.: The influence of temperature on the equilibrium between oxygen and haemoglobin of various forms of life, Jr. Physiol., 1925, lx, 428–442.
37. MACCALLUM, A. B.: Quoted by Rich.
38. MEAKINS, J. C.: Observations on the gases in human arterial blood in certain pathological pulmonary conditions, and their treatment with oxygen, Jr. Path. and Bacteriol., 1921, xxiv, 79–90.
39. MYERS, W. K., and KEEFER, C. S.: Relation of plasma proteins to ascites and edema in cirrhosis of the liver, Arch. Int. Med., 1935, lv, 349–359.
40. MYERS, W. K., and TAYLOR, F. H. L.: Hypoproteinemia probably due to deficient formation of plasma proteins: a study of one case, Jr. Am. Med. Assoc., 1933, ci, 198–200.
41. PELLEGRINI, G.: L'azione della sostanza tiroidea sulle proteine e sulla pressione colloido-osmotica del sangue e sulla diuresi nella cirrosi epatica con ascite, Arch. di Patolog. e Clin. Medica, 1934, xiii, 413–438.
42. PETERS, J. P., and EISENMAN, A. J.: The serum proteins in diseases not primarily affecting the cardiovascular system or kidneys, Am. Jr. Med. Sci., 1933, clxxxvi, 808–833.
43. PETERS, J. P., and VAN SLYKE, D. D.: Quantitative clinical chemistry. Volume I. Interpretations, 1931, Williams and Wilkins, Baltimore, 1264 pp.
44. RAY, G. B.: Chemical studies on the spleen. II. Changes in hemoglobin following removal of the spleen, Am. Jr. Physiol., 1928, lxxxvi, 138–144.
45. RAY, G. B., and STIMSON, B. B.: Observations on the chemical activity of the spleen. I. The relation of the spleen to methemoglobin in the blood, Am. Jr. Physiol., 1927, lxxxi, 62–73.
46. RAY, G. B., THOMAS, C. I., and STRONG, J. E.: The oxygenation of concentrated versus normal bloods, Jr. Clin. Invest., 1933, xii, 1051–1062.
47. RICH, A. R.: The pathogenesis of the forms of jaundice, Bull. Johns Hopkins Hosp., 1930, xlvii, 338–377.
48. RICH, A. R., and RESNIK, W. H.: On the mechanism of jaundice following pulmonary infarction in patients with heart failure, Bull. Johns Hopkins Hosp., 1926, xxxviii, 75–76.
49. RICHARDS, D. W., JR., and STRAUSS, M. L.: Oxy-hemoglobin dissociation curves of whole blood in anemia, Jr. Clin. Invest., 1927, iv, 105–126.
50. ROBSCHEIT-ROBBINS, F. S., and WHIPPLE, G. H.: Hemoglobin production factors in the human liver. II. Liver degeneration, cancer, cirrhosis, and hepatic insufficiency, Jr. Exper. Med., 1933, lvii, 653–670.
51. ROSIN, A.: Morphologische Organveränderungen beim Leben unter Luftverdünnung. Beitr. z. path. Anat. u. z. allg. Path., 1928, lxxx, 622–639.
52. ROWE, A. H.: The albumin and globulin content of human blood serum in health, syphilis, pneumonia, and certain other infections, with the bearing of globulin on the Wassermann reaction, Arch. Int. Med., 1916, xviii, 455–473.
53. RÜHL, A.: Über Störungen des Sauerstoffdurchtritts in der Lunge, Arch. f. exper. Path. u. Pharmakol., 1930, clviii, 282–303.

54. SALVESEN, H. A.: Variations in the plasma protein in non-renal conditions, Acta med. Scandin., 1929, lxxii, 113–123.

55. SAWADA, T.: Biochemical investigation of the blood in cases of experimental disturbance of liver function. Report II. Liver function and protein metabolism, Japan Jr. Gastro-Enterol., 1931, iii, 38–45.

56. SNELL, A. M., and ROTH, G. M.: The lactic acid of the blood in hepatic disease, Jr. Clin. Invest., 1932, xi, 957–971.

57. STARLINGER, W., and WINANDS, E.: Über das Verteilungsverhältnis der zirkulierenden Eiweizkörper im Verlaufe krankhafter Zustände. III. (Erkrankungen der Blut bildenden und zerstörenden Organe und der Leber, bösartige Geschwülste, Leukämie, Granulom, Magendarmgeschwür, Gastro-enteritis, Diabetes, und andere Erkrankungen der innersekretorischen Organe), Ztschr. f. d. ges. exper. Med., 1928, lx, 185–238.

58. STIMSON, B. B.: Changes in the oxygen capacity of the blood pigment of rabbits following splenectomy, Jr. Biol. Chem., 1927, lxxv, 95–99.

59. STIMSON, B. B., and HRUBETZ, M. C.: Changes in the oxygen capacity of the blood pigment of rabbits following partial hepatectomy, Jr. Biol. Chem., 1928, lxxviii, 413–415.

60. VAN SLYKE, D. D.: Note on a portable form of the manometric gas apparatus and on certain points in the technique of its use, Jr. Biol. Chem., 1927, lxxiii, 121–126.

61. VAN SLYKE, D. D., and NEILL, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement, Jr. Biol. Chem., 1924, lxi, 523–573.

62. WELLS, H. S., YOUMANS, J. B., and MILLER, D. G., JR.: A formula and nomogram for the estimation of the osmotic pressure of colloids from the albumin and total protein concentrations of human blood sera, Jr. Clin. Invest., 1933, xii, 1103–1117.

63. WHIPPLE, G. H.: Anemia, liver function, and hemoglobin production, Proc. Calif. Acad. of Med., 1932–1933, 81–102.

64. WIENER, J. H., and WIENER, R. E.: Plasma proteins, Arch. Int. Med., 1930, xlvi, 236–265.

HYPOTHYROIDISM: A COMMON SYMPTOM *

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The task to which I have set myself may be stated as follows: concentrating on a very small part of the endocrine system, I have tried with the aid of clinical tests and clinical experience to formulate some conclusions which are not at variance, I hope, with the best and soundest of theory and experimental data, and which have the virtue, I trust, of a firm basis on clinical facts. If anyone finds in this paper something exciting, fantastic or in the slightest degree revolutionary, I have signally failed in my purpose.

Some of us can remember the eager search for the cases of cretinism and of myxedema. It was the period when the findings at the postmortem table dominated medical thought almost without challenge. Generally speaking, all distributed function, physiological or chemical, was related as a matter of course to gross or microscopic anatomical changes. If actual changes were not demonstrable, it was a defect in technic, not in the theory. The prevailing thought of the times was entirely out of sympathy with any notion of transitory functional changes without evident organic change, or with the notion of mild persistent disturbances of any sort which could not finally be solved post mortem. In fact, our ideas of clinical medicine were largely the reconstructed pictures from the autopsy table.

To be sure, there were imaginative individuals who rebelled at this tyranny of morbid anatomy. One of the unfortunate effects of the early stages of emancipation from the rule of pathology was found in the fantastic and uncontrolled utterances of some of these in the field of endocrinology, which made this field a kind of plague spot in clinical medicine. However, the increasing influence of physiology, chemistry and also of bacteriology has had the effect of changing markedly the attitude of the best current clinical thought. Attention has shifted from the end stage of disease (and indeed of life) towards the early phases of disease. Functional disturbances were studied with newly developed methods and technics. Now we find a situation in which functional studies are sometimes carried on with (unfortunately) total disregard of morbid structural changes.

These functional studies have now reached a point at which intelligent attention can be directed towards thyroid dysfunction of a degree far less than those clinical states known as cretinism, exophthalmic goiter, and myxedema. In the laboratory new types of scientists have appeared, working with new methods, new materials, and all kinds of animals.

Clinical data were rapidly collected. The simple formula that a high basal metabolic rate equalled an operation, and that a low basal metabolic rate equalled thyroid administration, and that the results of both of these

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

equations meant cure, was early discarded. Gradually we have begun to organize, digest and classify our data and experiences. Here I shall omit all reference to the over-active function of the thyroid gland and shall confine my attention exclusively to the dysfunction which represents the apparent under-activity of the thyroid gland. Furthermore, in this discussion we shall eliminate all cases of organic disease of the endocrine system and also such cases of frank clinical disorders of the thyroid as myxedema and corresponding disorders of the other members of the endocrine system. It is perhaps open to argument whether a more exact and more suitable title might not be "Low Metabolic Rate, a Common Symptom." In truth the low metabolic rate is usually the determining factor in the discussion. However thyroid therapy has had an important rôle in these observations. In some instances basal metabolic rates have been ignored and thyroid administration employed. Again, the basal metabolic rate has frequently seemed to serve rather as a first approximation and not as an exact test. Consequently the old term, hypothyroidism, has been retained.

Certainly some families have many instances of dysfunction of the thyroid gland. These can often be related to general glandular unbalance. In addition to this, we sometimes find a persistently low metabolic rate, which may be taken roughly as evidence of hypothyroidism, in a substantial proportion of the members of a family. Many of these people seem entirely well. Such individuals do not conform to any particular type. They do not correspond to any notion of early or latent myxedema. They are as often thin as stout. The skin may be moist, the hair fine and glossy, and the pulse may be rapid. In others, there seems to be no connection between their particular ailments and the low thyroid activity, and furthermore, the administration of thyroid extract in various ways does not help the symptoms. In a small group thyroid therapy with the elevation of the basal metabolic rate to normal or a low normal figure seems to be associated with an improvement in general well-being.

By far the commonest association with a low metabolic rate (and by that I mean less than minus 15 per cent) is the condition perhaps most clearly designated as debility, when, of course, not associated with fever or growing neoplasm. The thought at once suggests itself that the thyroid gland shares in the general dysfunction of all the organs in the body, and that perhaps the lowered thyroid function is a general indicator of the total bodily function. However, there seems to be no precise parallelism between hypothyroidism and debility. Furthermore, the administration of thyroid and the apparent correction of the hypothyroidism may vary in the subjective effect on the patient from no result to a result indicating an apparent cure. Curiously enough the patient sometimes behaves differently under apparently similar conditions. One patient had a history of recurrent episodes of nervous fatigue or perhaps nervous exhaustion. In one of these episodes, the basal metabolic rate was as low as minus 40 per cent. Previous determinations had given low figures but near the line of normal. When

her rate was minus 40 per cent, energetic thyroid therapy was accompanied by a rapid restoration to satisfactory well-being. In subsequent episodes of similar symptoms, the basal metabolic rate was never again markedly low, and experimental thyroid therapy was never accompanied by any substantial improvement. In the various debilitated states due to many causes, some known and some unknown and often mixed, we have had similar experiences. As in many of the cases of familial hypothyroidism, these examples of hypothyroidism associated with debility present as a group none of the stigmata of myxedema. Actually most of the patients have been thin, and tachycardia of a mild degree has been common. Perhaps a substantial gain in weight has been the outstanding objective result of thyroid therapy in the successful cases. Subjectively the outstanding beneficial result has been improvement in general well-being. It should be emphasized again that apparently similar cases yield both successes and failures.

At one time thyroid therapy gained considerable favor in the treatment of chronic arthritis. Certainly, hypothyroidism is a frequent symptom of the associated debility of chronic arthritis, but presumably it is an associated symptom of the debility and not a causative factor. Of course, the correction of any symptom is indicated, and the subjective improvement thereby resulting, while varied, may be eminently satisfactory.

Our ideas are as yet far from clear as to the relation of the symptom of hypothyroidism to mental states. Doubtless, in many mental states there is an associated debility which in turn may be associated with the hypothyroidism of debility. On the other hand, it is becoming more evident that the individuality of a man with his physical, mental, nervous and behavior patterns, which all combine to make up his individual self and personality, is somehow closely linked with the structure and function of the endocrine glands, which of course represent the influence of heredity, environment, training and disease. Of course the thyroid gland is only one of the links of the chain of endocrine glands. Moreover, the relation of the thyroid and indeed of the whole endocrine system to various normal and abnormal mental states is not at this time clearly and definitely evident.

The interrelationship of the thyroid and some of the other endocrine glands is often demonstrable. Hypothyroidism is associated at times with female sterility, and thyroid therapy may be followed by pregnancy. Likewise, hypothyroidism may be seen in adolescence and in the menopause, and thyroid therapy may be distinctly beneficial. Its action is presumably indirect. The present advances in our knowledge of the various hormones may be fairly designated as exciting. In the experimental field the ability to achieve extraordinary results is literally breath-taking. It may well be that the near future has in store for us the solution of the complicated interrelationship of the endocrine glands. At this moment it seems that the rôle of the thyroid, so easily even if roughly tested, and when insufficient so easily restored by a simple therapeutic agent, may become perhaps relatively

insignificant. Just now, all endocrine roads lead to the pituitary, but for how long!

Probably attributable to some defect in these general glandular interrelationships, with perhaps debility as a further factor of possible importance, are a number of conditions which often but not always present evidence of hypothyroidism. Among these are amenorrhea or disturbed menstrual function; the various vasomotor disturbances, perhaps notably vasomotor rhinitis; some of the odd irregular slight fevers; some of the allergic states, some of the dermatoses, etc. In some of these, there is a definite hypothyroidism. Even when this exists, thyroid therapy is often not beneficial. It is undoubtedly inept to consider the hypothyroidism as the direct causative agent. The hypothyroidism may better be regarded as a symptom. Time does not permit of any elaboration of this variegated and miscellaneous group. It is only mildly helpful to our understanding of the situation to bring out that there is a family factor in some of these cases, a possible endocrine relationship in others, a presumable association with a debilitated state in another group and that some may be early or atypical manifestations of that clinical entity, which, when fully developed, we call myxedema. There are deep pitfalls for idle speculation and loose logic. It may even be too rash to claim that the dry skin on which a dermatologic lesion develops is a possible manifestation of early or latent myxedema. Certainly the intricate mysteries of vasomotor rhinitis are baffling. Here too we find in apparently similar cases the same discrepancies, namely those with and those without hypothyroidism and furthermore those which yield to treatment and those which do not. Again it is to be repeated that there is no precise parallelism between the level of the low basal metabolic rate and the success of thyroid therapy. As might be expected the lowest rates, in general, are often associated with the best therapeutic results, but excellent therapeutic results are sometimes obtained by the administration of thyroid to patients with essentially normal basal metabolic rates.

In further substantiation of these general views, the fact must be noted that thyroid therapy at times cannot be tolerated by these patients. Experience shows there are cases in which the administration of all the usual preparations of thyroid gland either (1) does not restore the basal metabolic rate to normal, (2) does not benefit the patient or (3) cannot be tolerated on account of such untoward symptoms as headache, palpitation, nervousness, etc.

Theoretically and experimentally the therapeutic administration of other glandular therapy has much to commend it in many of these groups of cases under discussion. Certainly a case of frank hypothyroidism, which is resistant to usual thyroid therapy, may well serve for clinical experimentation in glandular therapy. At present adequate clinical data are lacking for even tentative generalizations. However, there is a promise of other potent glandular therapeutic agents which time may show may supplement or even supplant thyroid therapy.

Hypothyroidism seems rarely to be a disease entity, but certainly, a common symptom. It is rather one of the fragments that make up the temporary or permanent pattern of the functional entity of the individual. As a fragment in a pattern it may have important relationships, most notably with the other endocrine glands. Presumably variations from the usual standard of the individual are more significant than variations from an arbitrary standard. In this respect there is some similarity to variations in blood pressure and especially to our interpretation of hypotension. All the theoretical, experimental and clinical data indicate that while hypothyroidism is only a symptom it is, nevertheless, a symptom which should be and can be frequently satisfactorily treated.

CLINICAL RELATIONSHIPS OF BLOOD CHOLESTEROL WITH A SUMMARY OF OUR PRESENT KNOWLEDGE OF CHOLESTEROL METABOLISM *

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ALTHOUGH much has been written about cholesterol, little is actually known of its metabolism. The amount in the blood and various organs is known, points of secretion and excretion have been located, and its various forms have been identified; yet its true function in the body is pretty much a mystery. While the determination of blood cholesterol has clinical value, there is still much to be learned regarding the behavior of cholesterol in the body under normal and pathological conditions.

Cholesterol itself is an unsaturated secondary alcohol, water insoluble, and although associated intimately with fat metabolism it is not a true lipid. The cholesterol present in the body is in part derived from that contained in ingested animal food, but the greater part is formed by synthesis within the organism. It is not derived from vegetable foods as plants are incapable of cholesterol synthesis.[1]

The following chart indicates the paths of cholesterol in the body as known at the present time.

The functions which have been ascribed to cholesterol are as follows [2, 24]:

1. A constituent of the framework of cell because of its stability to ordinary chemical change
2. A protective substance in cells, exerting its effect as:
   - An anti-toxic, anti-hemolytic and anti-infectious agent
   - An insulator of the central nervous system
   - A conditioning constituent of the skin
3. A conveyor of fatty acids to and from fat deposits
4. A facilitator of fat absorption

From the clinical point of view we are interested chiefly in the causes of variations in blood cholesterol, in the reasons for abnormal cholesterol deposits, especially in atherosclerosis, and in the mechanism of formation of cholesterol gall stones.

Even though we know comparatively little concerning the metabolism of cholesterol in the body, it is, nevertheless, possible to suggest how abnormal variations might arise. The following possibilities are suggested:

1. Abnormal synthesis beyond normal tolerance or destruction;

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2. Abnormal affinity of tissues for cholesterol, causing retention, including phagocytosis [3];
3. Abnormal precipitation or liberation;
4. Hemoconcentration or dilution [35];
5. Failure of destruction;
6. Failure of elimination.[3]

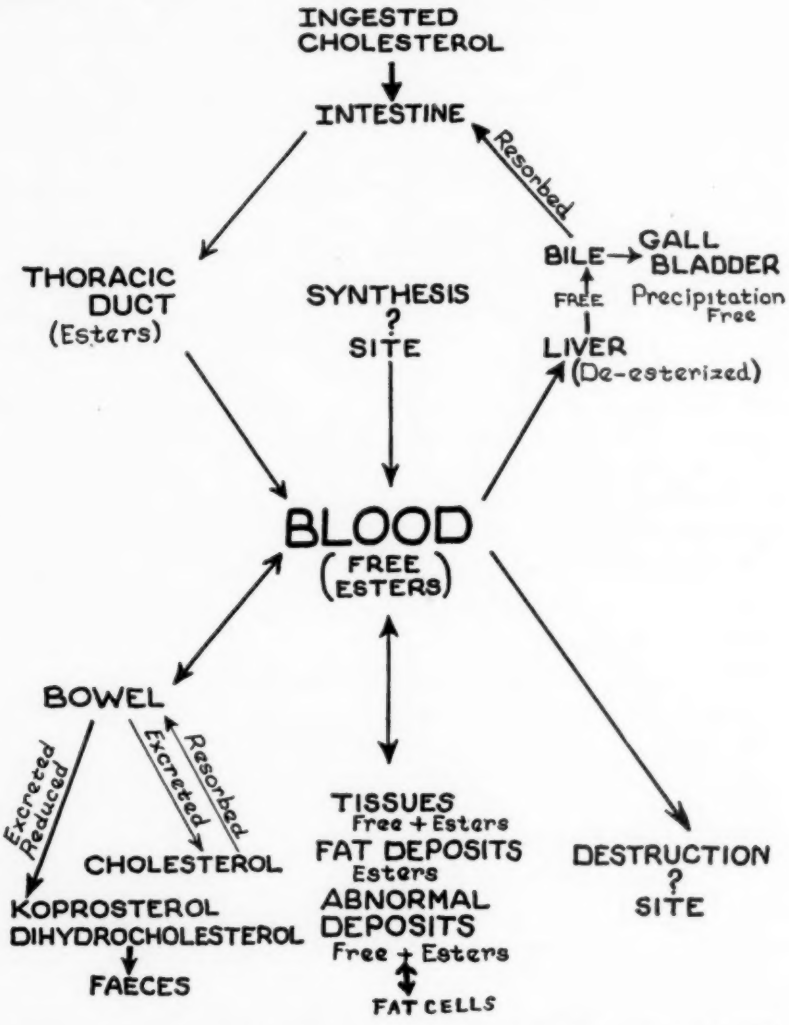

CHART. 1. Cholesterol paths in the body. (This chart is derived from the work of Windaus, Thannhauser, and Schönheimer abroad and Bloor, Speery and others in this country.)

An attempt will be made here to correlate these possible abnormalities in the cholesterol mechanism with clinical states wherein cholesterol metabolism appears to be disturbed.

Mechanism of Cholesterol Deposits

Cholesterol exists in the blood as such and also as cholesterol esters. The ester fraction of the total cholesterol under normal conditions varies from 40 to 60 per cent of the total. Likewise in the tissues, the cholesterol-ester ratio is of about the same proportion. In the blood cholesterol is thought to be present in colloidal suspension or linked with blood proteins. Almost all abnormal cholesterol deposits are associated with groups of fat or foam cells which are supposedly of reticulo-endothelial origin. There are two theories regarding the mechanism of abnormal cholesterol deposits:

1. Precipitation of cholesterol in the blood, phagocytosis there by the reticulo-endothelial cells, which thus become fat cells, and migration of these cells into the tissues, where they may degenerate, thus liberating cholesterol.[15]

2. Infiltration of tissues by cholesterol because of their altered permeability due to disease, and ingestion in the tissues by reticulo-endothelial cells of the deposited cholesterol; the fat cells thus forming at the site where they are found.[4]

Atherosclerosis

Atherosclerosis is not necessarily a senile disturbance.[4] While we cannot expect to overcome senility, there should be hope of preventing premature arteriosclerosis.[5, 19] Aside from hereditary, infectious and pressure phenomena, the evidence for a causal relation of cholesterol to atherosclerosis may be summarized as follows:

1. Atherosclerotic plaques contain cholesterol, the amount of which increases with the extent of atherosclerosis.[6]

2. The cholesterol content of the blood increases with age and with the extent of atherosclerosis.[7, 8, 9, 10, 13]

3, Atherosclerosis analogous to human atherosclerosis may be produced in rabbits by feeding cholesterol in large or small amounts.[11, 14, 15, 16, 9, 21]

4. Atherosclerosis is more frequent in conditions such as diabetes mellitus and myxedema in which there is an abnormally [14] high cholesterol content in the blood.[5, 17, 19]

No definite conclusion may be drawn in regard to dietary differences of races on the present data.[6, 18] Individual differences of diet within the race must be considered along with other predisposing or restraining causes.

It is of interest that it has been noted in the experimental production of cholesterol atherosclerosis that the simultaneous administration of dried thyroid or potassium iodide with cholesterol will prevent the occurrence of atherosclerosis.[20, 21] European investigators [9, 22, 23] see in this the rationale for the time honored use of potassium iodide and more recently of thyroid extract in the treatment of clinical arteriosclerosis. Rosenthal [6] has warned against the use of iodine, but its widespread use over many years would suggest that its dangers are insignificant.

Diets made up exclusively of animal foodstuffs with high fat content will

increase the cholesterol of the blood,[25] and a vegetable diet has been found to decrease the blood cholesterol in xanthomatosis.[3] The ability to tolerate cholesterol must vary in different individuals. It is conceivable therefore that in the presence of an inadequate cholesterol tolerance of whatever cause, a diet high in cholesterol may hasten the development of human atherosclerosis, particularly if such predisposing causes as diabetes, hypertension or toxic or nervous influences are present. In other words, predisposing causes pave the way for cholesterol deposits, and one might assume that the less cholesterol available, the less the atherosclerotic change.

The part cholesterol plays in atherosclerosis may be belittled, but much remains to be learned by clinical observation and experimentation, both of which have not kept pace with experimental work on animals.

Xanthoma and Xanthomatosis

Skin xanthoma and xanthelasma contain cholesterol and fatty deposits. Fat or foam cells are conspicuous in these lesions.[27] Hypercholesterolemia is a frequent finding in xanthomatosis with or without the presence of diabetes with which it is so commonly associated. Adequate treatment of an associated diabetes may cause absorption of the xanthomatous lesions.[17, 26, 35] Schönheimer [3] has shown in one carefully studied case of hypercholesterolemia and xanthomatosis that the retention of cholesterol was due to a defect in excretion. The high total cholesterol value was due to the ester fraction. On a strictly plant diet the total cholesterol content of the blood was markedly lowered, the change occurring entirely in the ester content. Wile, Eckstein and Curtis [62] believe that cholesterol is only a secondary factor in xanthoma formation. Several cases reported by them had normal blood cholesterol values. Low caloric diets were most successful in reducing xanthomatous deposits in their cases.

Xanthomatosis may occur in the bones and other tissues as well as in the skin.[58] Such conditions too are known to be associated with extensive accumulation of fat cells. In these diseases, too, the blood cholesterol may be elevated.[58, 63] Desiccated thyroid may have a favorable influence upon the absorption of these lesions, and should be more often given a trial.

With the disappearance of some xanthomata following treatment and the reversion of atheromatous changes in animals,[28] and possibly in humans,[4] the possibilities of low or cholesterol-free diets should be further investigated. In the authors' experience a diet free from animal-derived foods is not disagreeable and may be well tolerated.

Diabetes Mellitus

Hypercholesterolemia and hyperlipemia are common findings in diabetes only when the disease is uncontrolled. Since the use of insulin the serious prognosis of the patient with hyperlipemia has changed.[29] Blood choles-

terol and blood lipids in diabetics are now usually found within the normal range.[30, 31, 32, 33]

When cholesterol values of the blood over 400 mg. per 100 c.c are found, it usually indicates serious complications either present or imminent.[34] Especially is this true in juvenile diabetes. In a recent study of diabetic children by White and Hunt, 11 out of every 12 children with hypercholesterolemia showed either arteriosclerosis, retinitis, abscesses or lipemia retinalis.

A low blood cholesterol in a diabetic, on the other hand, may be of grave significance [34] indicating some associated disease as, for example, tuberculosis. Such patients do not live as long as the average diabetic.

In diabetic acidosis high blood cholesterol values are found, the highest observed being 1420 mg. per 100 c.c. with a total blood lipid content of 19.9 per cent. Adequate treatment is followed by a rapid fall. There appears to be no parallelism among the degree of acidosis, the blood sugar and the hypercholesterolemia.

The cause of hypercholesterolemia in diabetes is not clear. The marked rise in some cases of acidosis is thought by Man and Peters [35] to be due to hemoconcentration. This, however, does not explain hypercholesterolemia in diabetes without acidosis. In diabetes with arteriosclerosis there is an increased ester content,[13] and there is evidence indicating that hypercholesterolemia and arteriosclerosis in diabetes may be influenced by the fat content of the diet.[5] In any event cholesterol deposits do occur as manifested by xanthomatosis, gall stones, and arteriosclerosis.[17] Adequate treatment will cause absorption of xanthomatous lesions, but whether early atheromatous lesions disappear is not known. The aim of diabetic therapy now is the prevention of, or retardation of, arteriosclerotic changes. Control of blood cholesterol may play an important rôle in accomplishing this.[64]

Lipoid Nephrosis

In this disease there is a marked deposition of fat in the kidneys and liver and to a lesser extent in other organs.[36] Fat cells are found but are not prominent. Blackman [37, 38] has been able to produce lipoid nephrosis in rabbits by the injection of pneumococcus toxin. He suggests that lipoids, and hence cholesterol, are liberated as the result of cellular destruction by the toxin rather than through any change in cholesterol metabolism. Gainsborough [36] believes hypercholesterolemia in this disease is related to disturbed blood proteins. Blackman's clinical observations strongly suggest a relationship between chronic pneumococcus infections and lipoid nephrosis. The increase in blood cholesterol is due to an increase both in esters and free cholesterol. The determination of blood cholesterol in this disease is helpful in diagnosis. Curiously, according to Gainsborough and others,[36] the feeding of thyroid has little effect on lowering the blood cholesterol.

Thyroid Disease

Hyperthyroidism causes a drop in blood cholesterol while hypothyroidism brings about a marked increase.[10, 12, 39,40,41] Hypercholesterolemia in thyroid deficiency may be partly due to retention of cholesterol through diminished secretion in bile and lowered excretion in the intestinal tract. In animals, experimental hypothyroidism causes a low cholesterol content in the bile. With Wilkinson [51] we have found the same to be true in cases of myxedema. In hyperthyroidism, on the other hand, the cholesterol content of the bile has been normal or high. It does not seem likely, however, that the total change in blood cholesterol in thyroid diseases can be accounted for by this finding alone. As a rule in myxedema there is a decrease in esters and an increase in free cholesterol.[40]

That these variations in cholesterol are due to variations in thyroid activity and not due to variations in total body metabolism is shown by the fact that hypometabolism from other or unknown causes is usually not associated with the abnormally high blood cholesterol values found in myxedema.[42] Elevation of metabolism by dinitrophenol is not accompanied by a corresponding drop in blood cholesterol [43] as it is in hyperthyroidism. Blood cholesterol determinations are, therefore, useful in differential diagnosis and in treatment of thyroid disease, especially hypothyroidism.

The relationship of thyroid deficiency and hypercholesterolemia to atherosclerosis deserves mention. Here again we have a condition long known to be favorable to the development of arteriosclerosis, both clinically and experimentally.[19] I have already spoken of the prevention of cholesterol atherosclerosis in rabbits by thyroid feeding. Leary suggests that the possible waning secretion of the thyroid in later life may contribute to atheromatous changes.[15]

Hypopituitarism and the Pituitary-Thyroid Relationship

It is well known that pituitary deficiency is accompanied by a low metabolic rate. This has often been referred to as pituitary myxedema. It has been suggested that this is the result of a deficiency of the anterior pituitary thyrotropic hormone which so profoundly influences the activity of the thyroid. Clinically there are many differences between hypopituitarism and myxedema. This led us to investigate the behavior of the blood cholesterol in hypopituitarism. Since the basal metabolic rate in this condition is as low and often lower than in myxedema, we felt there should be a corresponding rise in blood cholesterol if the low metabolic rate was entirely due to thyroid deficiency. Fourteen cases of hypopituitarism due to verified chromophobe tumors were studied from this point of view. Of these 14 cases, only two showed a blood cholesterol of over 240 mg. per 100 c.c. The average values are shown in the table.

	Hyperthyroidism	Acromegaly	Nonhyperthyroid	Myxedema	Hypopituitarism
No. of cases	283	2	146	47	14
Blood cholesterol mg. per cent (average)	134	156	179	355	209
B.M.R. per cent (average)	+45	+19	+0	−26	−28

Thus clinical facts do not tally with experimental work. One must, therefore, assume that the low metabolism in hypopituitarism is not solely of thyroid origin and that myxedema is primarily a disease of the thyroid. As Evans [44] points out, myxedema may be compared to the menopause, since excess thyrotropic hormone of pituitary origin has been reported in myxedema, just as excess pituitary gonadotropic hormone is found at the menopause.[45]

Biliary System

Free cholesterol is found in the bile, and according to Schönheimer and Hrdina [46] it is in loose combination with bile acids, forming a complex which is capable of absorbing even greater quantities of cholesterol. Ingested cholesterol is thought to be absorbed through the excess of bile acids in this complex.

Time will not permit a discussion of the various opinions as to the mechanism of cholesterol deposits in the gall-bladder.[46, 47, 48, 49, 50] It is sufficient to say that cholesterol is precipitated in the gall-bladder cavity and that such precipitation is probably the basis for cholesterol stone formation. Cholesterol deposits in the gall-bladder wall, the so-called cholesterolosis of the gall-bladder, is accompanied by collections of fat cells. No adequate proof exists, however, that cholesterol is or is not secreted or absorbed by the gall-bladder mucosa. Wilkie [48] believes that hypercholesterolemia in dogs is followed by passage of cholesterol from the blood through the gall-bladder mucosa into the gall-bladder, and that if there is a low blood cholesterol, cholesterol will pass from the gall-bladder into the blood. Deductions from experimental work on dogs are hardly valid in view of the nonoccurrence of gall stones in these animals. It would seem advisable to take advantage of long standing biliary fistulae in human subjects to throw more light upon this question. The rationale of dietary management with low cholesterol diets [5] hinges upon this problem. It is doubtful that such passage actually takes place.[46] It is conceivable, however, that cholesterolosis of the gall-bladder wall might regress by diet in view of the similarity of the process to xanthomatous lesions. Of interest in connection with cholesterol gall stones or precipitated cholesterol in the gall-bladder cavity is the fact that feeding certain bile acids increases the bile acid secretion without increasing the cholesterol content of the bile.[54] Such excess of bile acids might dissolve precipitated cholesterol or cholesterol stones, in much the

same manner as a cholesterol stone can be dissolved in a dog's gall-bladder where the cholesterol in the cholesterol-bile acid complex is exceedingly low.[46]

The hypercholesterolemia of biliary obstruction often affords a useful diagnostic aid in the differential diagnosis of the cause of jaundice. The increase in the blood is in both free cholesterol and esters although the latter do not parallel the former. Any infection tends to counteract hypercholesterolemia, even when obstructive jaundice is present. In degenerative disease of the liver with marked jaundice the cholesterol is lowered, the chief drop being in the esters,[55] a very low or absent ester content being present in the rapidly fatal cases. That the hypercholesterolemia of obstructive jaundice is a purely mechanical effect is doubted by some.[56] The lowered cholesterol ester in degenerative disease is thought due to injury to the esterifying power of the liver cells,[57] although this view is not universally accepted.[56] Removal of the liver does not cause a drop in blood cholesterol ester content; in fact higher values are found.[59]

Hypercholesterolemia

Not infrequently a high blood cholesterol is found without evidence of the usual diseases of which it is characteristic. In our experience such findings have occasionally revealed unrecognized myxedema. Experience with total thyroidectomy for heart disease, as well as subtotal thyroidectomy for hyperthyroidism, has taught us that a high degree of thyroid deficiency may exist without the usual external manifestation of the condition. Thus a high blood cholesterol may be of clinical value, especially when metabolism tests are unsatisfactory, as for example in children.

On the other hand hypercholesterolemia is occasionally found with low metabolic rates, and while this must be considered presumptive evidence of thyroid deficiency, and as indication for a therapeutic trial of thyroid extract, the results of treatment do not always prove as satisfactory as they do in myxedema. We have found this combination in a few apparently healthy individuals under 40 years of age.

As a rule, hypercholesterolemia is found in individuals over 40 or 50 years of age.[6-10] A proportion of these cases display undoubted arteriosclerosis. Early senility may simulate in some instances a mild thyroid deficiency, and at times it is difficult to decide which is present, if not both. Administration in the beginning of not more than 1 grain of desiccated thyroid U.S.P. daily may be well tolerated, often diminishing the blood cholesterol and producing clinical improvement. This, of course, should not be interpreted as always indicating thyroid deficiency.

Further studies should be made of these individuals with hypercholesterolemia. The cholesterol-ester ratio should be determined, the effect of thyroid, iodide and bile acid feeding investigated, and the bile and feces studied. The effect of cholesterol-free diets in hypercholesterolemia is worthy of further investigation.

In this paper we have not attempted to present the reports of various

investigators on minor variations of blood cholesterol. The effect of fever, sunlight, vitamins, adrenalin, liver and spleen ablation, anemia and pregnancy and many other measures have been studied. These variations rarely exceed the normal limits of blood cholesterol values which are wide. Differences in methods of determining blood cholesterol may give wide variations in results. Thus each laboratory should set its own standards for the normal range of total cholesterol, which is usually from 120 to 230 mg. per 100 c.c. At times this appears too wide a range, at other times it seems too narrow. It is safe to say, however, that a value of 300 mg. per 100 c.c. or more must be considered above the average, but as to whether it is abnormal in all cases has as yet not been determined.

Summary

1. Determination of blood cholesterol and cholesterol esters has clinical value.

2. Abnormal cholesterol deposits in the various tissues of the body bear a close resemblance, and on the whole are accompanied by higher blood cholesterol values. While the evidence suggests that inability of the organism to handle cholesterol properly is the cause of these lesions, it is still not entirely convincing from all standpoints. This theory must be considered a working hypothesis which further clinical investigation should prove or disprove.

BIBLIOGRAPHY

1. Schönheimer, R.: New contributions in sterol metabolism, Science, 1931, lxxiv, 579–584.
2. Bills, C. E.: Physiology of sterols, including vitamin D, Physiol. Rev., 1935, xv, 1–97.
3. Schönheimer, R.: Über eine Störung der Cholesterin-Ausscheidung (Ein Beitrag zur Kenntnis der Hypercholesterinämien), Ztschr. f. klin. Med., 1933, cxxiii, 749–763.
4. Aschoff, L.: Arteriosclerosis (Edited by Cowdry, E. V.), 1933, Macmillan Co., N. Y., p. 1.
5. Joslin, E. P.: Arteriosclerosis and diabetes, Ann. Clin. Med., 1927, v, 1061–1080.
6. Rosenthal, S. R.: Studies in atherosclerosis, I and II, Arch. Path., 1934, xviii, 473; III and IV, 660; V, 827–842.
7. Mjassnikow, A. L.: Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, Ztschr. f. klin. Med., 1925, cii, 65–78.
8. Parhon, C. J., and Parhon, M.: L'Hypercholesterinemie de la vieillesse, Comp. rend. Soc. de biol., 1923, lxxxviii, 231.
9. Gordonoff, T., and Zurukzoglu, S.: Cholesterin, Ergosterin, und Gefässsklerosen, Schweiz. med. Wchnschr., 1934, lxiv, 284–289.
10. Hurxthal, L. M.: Blood cholesterol in thyroid disease: analysis of findings in toxic and non-toxic goiter before treatment, Arch. Int. Med., 1933, li, 22–32.
11. Anitschkow, N., and Chalatow, S.: Über experimentelle Veranderungen der Kaninchen-Aorta bei Cholesterinsteatose, Beitr. z. path. Anat. u. z. allg. Path., 1913, lvi, 379.
12. Hurxthal, L. M.: Blood cholesterol in thyroid disease. II. Effect of treatment, Arch. Int. Med., 1933, lii, 86–95.
13. Gibbs, C. B. F., Buckner, E., and Bloor, W. R.: Cholesterol to cholesterol ester ratio in plasma of diabetics with advanced arteriosclerosis, N. E. Jr. Med., 1933, ccix, 384–386.
14. Anitschkow, N.: Experimental cholesterin atherosclerosis, historical data (*in* Arteriosclerosis by Cowdry, E. V.), 1933, Macmillan Co., N. Y., p. 281.

15. LEARY, T.: Experimental atherosclerosis in rabbit compared with human (coronary) atherosclerosis, Arch. Path., 1934, xvii, 453–492.
16. ANITSCHKOW, N.: Zur Ätiologie der Atherosclerose, Virchow's Arch. f. path. Anat., 1924, ccxlix, 73–82.
17. WARREN, S.: The pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia, pp. 119.
18. WEISS, S., and MINOT, G. R.: Nutrition in relation to arteriosclerosis (*in* Arteriosclerosis by COWDRY, E. V.), 1933, Macmillan Co., N. Y., p. 233.
19. EISELSBERG, PICK, PINELES, BIEDL, RÖSSLE, and MARESCH: Quoted by GORDONOFF and ZURUKZOGLU.[9]
20. LIEBIG, H.: Experimentelle Untersuchungen über die Jodwirkung auf die Atherosklerose, Med. Klin., 1929, xxv, 1100.
21. TURNER, K. B.: Studies on prevention of cholesterol atherosclerosis in rabbits; effects of whole thyroid and of potassium iodide, Jr. Exper. Med., 1933, lviii, 115–125.
22. PARHON, C. I., and ORNSTEIN, I.: Influence de la thyroxine sur la cholestérolémie et la lipémie, Comp. rend. Soc. de biol., 1931, cviii, 303–304.
23. LEVY, M., and LEVY, E.: Le traitment de l'hypercholestérolémie par la thyroxine, Presse méd., 1932, xl, 240–242.
24. STARLING, E. H.: Principles of human physiology, 1930, Lea and Febiger, Philadelphia, p. 42.
25. TOLSTOI, E.: Effect of exclusive meat diet on chemical constituents of the blood, Jr. Biol. Chem., 1929, lxxxiii, 753–758.
26. MCGAVACK, T. H., and SHEPARDSON, H. C.: Xanthoma accompanied by hypercholesterolemia, ANN. INT. MED., 1933, vii, 582–604.
27. PLEWES, L. W.: Nature and origin of xanthoma cell, Arch. Path., 1934, xvii, 177–186.
28. ANITSCHKOW, N.: Das Wesen und die Entstehung der Atherosclerose, Ergebn. d. inn. Med. u. Kinderh., 1925, xxviii, 1–46.
29. JOSLIN, E. P., BLOOR, W. R., and GRAY, H.: Lipoids in diabetes, Jr. Am. Med. Assoc., 1917, lxix, 375.
30. HUNT, H. M.: Cholesterol in blood of diabetics treated at New England Deaconess Hospital, N. E. Jr. Med., 1929, cci, 659–667.
31. WHITE, P., and HUNT, H. M.: Cholesterol of blood of diabetic children, N. E. Jr. Med., 1930, ccii, 607–616.
32. RABINOWITCH, I. M.: Cholesterol content of blood plasma as index of progress in insulin treated diabetics, Canad. Med. Assoc. Jr., 1927, xvii, 171–175.
33. HUNT, H. M.: Unpublished data.
34. JOSLIN, E. P.: What cholesterol means to me in the treatment of my diabetics, Proc. Interstate Postgrad. Med. Assemb. N. Am., 1935. (In press.)
35. MAN, E. B., and PETERS, J. P.: Lipoids of serum in diabetic acidosis, Jr. Clin. Invest., 1934, xiii, 237–261.
36. GAINSBOROUGH, H.: A study of the so-called lipoid nephrosis, Quart. Jr. Med., 1930, xxiii, 101.
37. BLACKMAN, S. S., JR.: Pneumococcal lipoid nephrosis and relation between nephrosis and nephritis; clinical and anatomical studies, Bull. Johns Hopkins Hosp., 1934, lv, 1–56.
38. BLACKMAN, S. S., JR.: Pneumococcal lipoid nephrosis and relation between nephrosis and nephritis; experimental studies, *ibid.*, lv, 85–130.
39. MASON, R. L., HUNT, H. M., and HURXTHAL, L. M.: Blood cholesterol values in hyperthyroidism and hypothyroidism; their significance, N. E. Jr. Med., 1930, cciii, 1273–1278.
40. SCHWARZ, H., and TOPPER, A.: Cholesterol partitions of blood in myxedema, Jr. Pediat., 1933, iii, 242–246.
41. HURXTHAL, L. M.: Blood cholesterol and thyroid disease. III. Myxedema and hypercholesterolemia, Arch. Int. Med., 1934, liii, 762–781.

42. HURXTHAL, L. M.: Blood cholesterol and hypometabolism, Arch. Int. Med., 1934, liii, 825–831.
43. CUTTING, W. C., RYTAND, D. A., and TAINTER, M. L.: Relationship between blood cholesterol and increased metabolism from dinitrophenol and thyroid, Jr. Clin. Invest., 1934, xiii, 547–552.
44. EVANS, H. M.: Growth hormone of anterior pituitary, Jr. Am. Med. Assoc., 1935, civ, 1232–1237.
45. ARON, M.: Le titrage des hormones préhypophysaires dans l'urine humaine; son intérêt dans l'exploration functionelle des diverses glandes endocrines, Bull. Acad. de méd., 1934, cxi, 273–275.
46. SCHÖNHEIMER, R., and HRDINA, L.: Etiology of gall stones; chemical factors, Proc. Soc. Exper. Biol. and Med., 1931, xxviii, 944–945.
47. ANDREWS, E., DOSTAL, L. E., and HRDINA, L.: Etiology of gall stones; is cholesterol excreted by the gall-bladder mucosa? Arch. Surg., 1933, xxvi, 382–388.
48. WILKIE, A. L., and DOUBILET, H.: Passage of cholesterol through mucosa of gall-bladder, Arch. Surg., 1933, xxvi, 110–121.
49. WEISER, H. B., and GRAY, G. R.: Mechanism of formation of pure cholesterol gall stones, Arch. Path., 1934, xvii, 1–9.
50. RAVDIN, I. S., RIEGEL, C., JOHNSTON, C. G., and MORRISON, P. J.: Studies in biliary tract disease, Jr. Am. Med. Assoc., 1934, ciii, 1504–1509.
51. WILKINSON, S. A., HURXTHAL, L. M., and HUNT, H. M.: Unpublished data.
52. LEITES, S., and ISABOLINSKAJA, R.: Veränderungen in Gallenchemismus und Sekretion unter dem Einfluss des Thyroxins, Klin. Wchnschr., 1933, xii, 149–150.
53. TWISS, J. R., and GREENE, C. H.: Dietary and medical management of diseases of gall-bladder, Jr. Am. Med. Assoc., 1933, ci, 1841–1847.
54. WRIGHT, A., and WHIPPLE, G. H.: Bile cholesterol fluctuations due to diet factors, bile salt, liver injury, and hemolysis, Jr. Exper. Med., 1934, lix, 411–425.
55. EPSTEIN, E. Z.: Cholesterol of blood plasma in hepatic and biliary diseases, Arch. Int. Med., 1932, l, 203–222.
56. GARDNER, J. A., and GAINSBOROUGH, H.: Blood cholesterol studies in biliary and hepatic disease, Quart. Jr. Med., 1930, xxiii, 465–483.
57. THANNHAUSER, S. J., and SCHABER, H.: Über die Beziehungen des gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, Klin. Wchnschr., 1926, v, 252.
58. SHEELING, M. D., and VOSHELL, A. F.: Xanthomatosis generalisata ossium: report of a case simulating osteitis fibrosa cystica, Arch. Int. Med., 1933, lv, 592.
59. THANNHAUSER, S. J.: Die chemischen Leistungen der normalen Leber für die Vorgänge des intermediären Stoffwechsels, Klin. Wchnschr., 1933, xii, 49–54.
60. JOSLIN, E. P.: Treatment of diabetes mellitus, 5th ed., 1935, Lea and Febiger, Philadelphia.
61. MCGAVACK, T. H., and SHEPARDSON, H. C.: Xanthoma accompanied by hypercholesterolemia occurring in otherwise normal individual and in individual with acromegaly and diabetes, ANN. INT. MED., 1933, vii, 582–604.
62. WILE, U. J., ECKSTEIN, H. C., and CURTIS, A. C.: Lipid studies in xanthoma: further contribution, Arch. Dermat. and Syph., 1929, xix, 35–51. Lipoid studies in xanthoma: further contribution, *ibid.*, xx, 489–500.
63. ROWLAND, R. S.: Anatomies of lipid metabolism, Oxford Medicine, iv, 2143.
64. RABINOWITCH, I. M.: Arteriosclerosis in diabetes, ANN. INT. MED., 1935, viii, 1436–1474.

BLOOD CHOLESTEROL IN DISTURBANCES OF THE BASAL METABOLIC RATE *

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BIOCHEMICAL studies in the metabolism of sterols have resulted in the accumulation of a vast amount of information concerning sterol content (usually recorded as cholesterol, either free or combined) of foodstuff, blood, tissues in general, and excretions. Little of this information can as yet be taken as fitting evidence in a hypothesis of the function of and intermediary metabolism of cholesterol. Clinical studies for a score of years have been appearing at an increasing rate until at present there are available blood cholesterol figures for the majority of diseases. Yet there is little diagnostic or prognostic information obtained from a knowledge of the blood cholesterol level that is not better obtained by other clinical studies of a given disease process.

The "sine qua non" of blood chemical studies for a clinician, i.e., a rapid, inexpensive, reasonably accurate method of estimation of a given constituent in a small volume of blood, appeared, in the case of cholesterol, in 1916. In that year, Bloor,[1] doyen of American biochemists in the field of fat metabolism, published a method for the extraction of lipoids and the precipitation of proteins in an alcohol-ether mixture. Subsequent to filtration and selective redissolving of the lipoid fraction by chloroform, the estimation of cholesterol and related sterols is made by colorimetric application of the Liebermann-Burchard reaction. In the clinical studies which followed the publication of the method, blood cholesterol alterations were reported in epilepsy, cancer, primary and secondary anemias, obesity, the nephrotic syndrome, nephritis, arteriosclerosis, diabetes, hepatic disease, physical exercise, types of lipemia, growing children, syphilis, feeble-mindedness, lipoid granulomatosis, infections such as scarlet fever and typhoid fever, toxemias of pregnancy, cholelithiasis, and, particularly in recent years, disease of the thyroid gland.

METHOD

For a period of two years the author made determinations of plasma cholesterol values in patients residing in Dallas County, Texas. The series, besides controls, comprises those patients having metabolic rate determinations in either Baylor University Dispensary or Parkland Hospital, and those drawn from private practice. The method used was that of Sackett,[2] a modification of the original Bloor [1] procedure. Its advantages, emphasized by the author, are found to be that: (1) less alcohol and ether are required; (2) less time is required for the determination; and (3) less blood is required for cholesterol estimation. Determinations were made on

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plasma which had been placed in a laboratory refrigerator for not more than 24 hours. It was demonstrated, however, that the total cholesterol values would remain constant for three or four days in plasma kept at low temperatures. All blood was drawn from fasting patients. The method determines "total cholesterol" and is to be distinguished from separate estimations for ester cholesterol and free cholesterol, a procedure involving the precipitation of the latter form by digitonin.[3, 4]

Results

In a control series of normal adults it is apparent that there are greater variations than the usual textbook figures for cholesterol values indicate. The majority of the controls were between 20 and 30 years of age. No sex difference appeared.

In 52 controls the values ranged from 150 to 228 mg. for 100 c.c. with a mean reading of 198 and an average of 193 mg. It may be observed that 63.5 per cent of the controls had values between 181 and 210 mg.

Table I

The Spread of Cholesterol Values in Normal Adults

Mg.	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.
Below 160	161–170	171–180	181–190	191–200	201–210	Above 210
2	6	4	8	9	16	7

From the group of patients who were seeking medical advice and whose metabolic rates were taken and found to be normal, we have arranged a second control group. No patient in this group had a diagnosis of thyroid disorder. There were few males in the group and a great majority of females were patients with symptoms of pelvic disease, menopausal disturbances or functional disorders of the nervous system. Fifty-eight patients, whose metabolic rate was neither greater than +10 nor less than —10, were selected at random. These showed a distribution of values that cover a somewhat wider range than the first control group. A table giving the sex, metabolic rate and diagnosis is appended.

The range was from 100 to 308 mg. per 100 c.c., with an average of 180 mg. per 100 c.c., from the comparatively greater number of cholesterol readings in the group of the lower level.

In the series studied there were 45 patients with a metabolic rate above +10. Five of these with rates above +50 had plasma cholesterol values of 182, 133, 168, 133 (the highest rate +89 and +91 on successive mornings) and 125 mg., respectively. Three of the values are undoubtedly in the abnormal group. Of five patients with metabolic rates between +40 and +50, the plasma cholesterol values were 162, 154, 188, 176, and 146 mg., respectively. From this group of 45 patients there could be selected 16 who had the history, symptoms and physical findings of undoubted thyrotoxicosis and who had been given such a clinical diagnosis.

TABLE II

Cholesterol Values in Patients with a Normal B.M.R.

B.M.R.	Race	Sex	Plasma Cholesterol	Clinical Diagnosis
−1	W	F	168 mg.	Cardiac disease
+8	C	F	232 mg.	Peptic ulcer
−5	W	F	178 mg.	Ovarian deficiency
−7	W	F	186 mg.	Chronic cholecystitis
+7	W	F	142 mg.	Neurosis
−2	W	F	182 mg.	Hypothyroid
+1	W	F	175 mg.	Obesity
−7	W	M	176 mg.	Varicose veins
−2	C	F	154 mg.	Pregnancy
−9	W	F	154 mg.	Chronic tonsillitis
−5	W	F	141 mg.	Obesity. Hunner's ulcer
−5	W	M	140 mg.	Obesity
−4	W	F	134 mg.	Simple goiter
+5	W	M	176 mg.	Cachexia
−10	W	F	164 mg.	Nephrosis
−2	C	F	196 mg.	Menstrual disturbances
−8	C	F	182 mg.	Salpingitis. Migraine
+4	W	F	210 mg.	Menopause syndrome
+2	W	F	163 mg.	Chronic tonsillitis
−8	W	F	243 mg.	Obesity
−3	W	F	120 mg.	Sterility
−4	W	F	143 mg.	Malnutrition
+5	C	F	136 mg.	Obesity. Varicose ulcers
−3	W	F	100 mg.	Sinusitis
−10	W	F	130 mg.	Pelvic infection
+6	C	M	164 mg.	Arthritis
+6	W	F	140 mg.	Pelvic infection
+2	C	F	143 mg.	
−9	W	F	188 mg.	Pyelitis
+5		F	168 mg.	Fibroid uterus
−10	C	F	200 mg.	Obesity. Varicose ulcers
+6	W	F	203 mg.	Obesity
−5	W	F	232 mg.	Endocrine dyscrasia
0	C	F	170 mg.	Salpingitis
−1	W	F	250 mg.	Chronic bronchitis
+9	W	F	136 mg.	Ovarian disorders
+2	W	F	144 mg.	Ovarian deficiency
−5	C	F	219 mg.	Salpingitis
+5	W	F	240 mg.	Obesity
−6	W	F	237 mg.	Salpingitis
+8	W	F	200 mg.	Menopause]
+6	C	F	150 mg.	Salpingitis. Obesity
−4	C	F	158 mg.	Syphilis
−1	W	F	182 mg.	Pelvic infection
+8	W	F	207 mg.	Infected teeth
+7	W	F	166 mg.	Obesity and C.N.S. syphilis
−6	C	F	140 mg.	Thyroid adenoma
−8	W	F	242 mg.	Psychoneurosis
+3	C	F	154 mg.	Salpingitis
−6	C	F	201 mg.	Endocervicitis
−2	C	M	171 mg.	Malnutrition
−2	C	F	211 mg.	Pelvic infection
−3	C	F	170 mg.	Rheumatic heart disease
−7	W	M	308 mg.	Irritable colon
−2	W	M	230 mg.	Arthritis
−2	C	F	222 mg.	Obesity
−3	W	F	239 mg.	
−7	W	M	280 mg.	Chronic glomerulonephritis

TABLE III

Spread of Cholesterol Values in Patients with Normal B.M.R.

Below 141 Mg.	Mg. 141–150	Mg. 151–160	Mg. 161–170	Mg. 171–180	Mg. 181–190	Mg. 191–200	Mg. 201–210	Mg. 211–220	Above 220 Mg.
9	6	4	8	5	5	3	4	1	7

TABLE IV

Patients with a Diagnosis of Hyperthyroidism

B. M. R.	Race	Sex	Cholesterol
+89	C	F	133 mg.
+91			
+37	W	F	120 mg.
+13	C	M	116 mg.
+50	W	F	176 mg.
+51	W	F	125 mg.
+18	W	F	130 mg.
+68	W	F	182 mg.
+49	W	M	162 mg.
+87	W	M	133 mg.
+42	W	F	154 mg.
+57	W	F	168 mg.
+38	W	F	280 mg.
+31			285 mg.
+36	W	F	143 mg.
			150 mg.
+40	W	F	158 mg.
+43	C	F	146 mg.
+40	C	M	153 mg.

It will be seen from the table that the plasma cholesterol values do not parallel the metabolic rate. There is a fair tendency to low cholesterol values, however. The one exceptionally high cholesterol value (cholesterol 280 mg., B.M.R. +38) deserves comment. The patient, Mrs. E. M., age 50, in 1932 became aware of weakness, moderate loss of weight, tachycardia and restlessness. For a period of 14 months she was treated by a physician for "heart disease." In bed during this treatment, she could gain a few pounds, felt well, and was not disturbed by tachycardia. But each time she was allowed out of bed (after a period of complete rest, sedatives, and the well-nigh omnipresent digitalis) her symptoms immediately returned. She changed physicians in 1933 at which time there was an exophthalmos, a diffuse thyroid enlargement, a heart rate of 128 with a regular rhythm and other signs of thyrotoxicosis. The first metabolic rate was +38. Two days later it was +31. The corresponding plasma cholesterol values were 280 mg. and 285 mg. Five days after the subtotal thyroidectomy, the plasma cholesterol was 345 mg. and the metabolic rate —2. Thirty-five days postoperatively, her metabolic rate was —20 and the plasma cholesterol 400 mg. Thyroid was given for a few weeks but was discontinued because she felt that as little as one half-grain daily made her nervous and conscious of her heart. Six months later the metabolic rate was +4, cholesterol 268 mg., and she had no complaints. Hence, while the expected shift in blood

cholesterol did occur with the change in the metabolic rate, the range was extremely well removed from our usual concept of a normal cholesterol value.

Comprising the group of patients with a metabolic rate lower than —10, there are 42 adults. Great variability and lack of consistency in plasma cholesterol values again occur as indicated in the general distribution.

TABLE V

The Spread of Cholesterol Values in Patients with B.M.R. Lower than — 10

Below 141 Mg.	Mg. 141–150	Mg. 151–160	Mg. 161–170	Mg. 171–180	Mg. 181–190	Mg. 191–200	Mg. 201–210	Mg. 211–220	Above 220 Mg.
6	2	5	5	7	2	4	3	1	7

There is a striking similarity between the distribution here and that of the group of patients with metabolic rates in the zone of —10 to +10. But a metabolic rate is a variable and unreliable device for classification. From this group there are 19 with symptoms and physical findings justifying a clinical diagnosis of myxedema or hypothyroidism. Such a diagnosis in these patients was not only justified by the recorded picture of the patient but also was proved by therapy with varying amounts of thyroid for a suitable period of time. A table of this group of 19 is given.

TABLE VI

Patients with a Clinical Diagnosis of Hypothyroidism

B.M.R.	Race	Sex	Plasma Cholesterol
−14	W	M	120 mg.
−19	W	F	154 mg.
−24	W	F	133 mg.
−21	C	F	226 mg.
−24	W	F	166 mg.
−25	C	M	180 mg.
−26	W	F	168 mg.
−15	W	F	168 mg.
−29	W	M	144 mg.
−33	W	F	147 mg.
−18	W	F	133 mg.
−36	W	F	182 mg.
−20	W	F	294 mg.
−18	W	F	226 mg.
−14	W	F	176 mg.
−31	W	F	222 mg.
−26	W	F	273 mg.
−25	W	F	176 mg.
−18	W	F	162 mg.

In this group suffering from hypothyroidism there are eight patients with a metabolic reading of —25 or lower. The plasma cholesterol values were determined to be 180, 168, 144, 147, 182, 222, 273, and 176 mg. respectively. Only two can be said to be elevated suggestively.

From a study of these tables one cannot find any tendency toward an

inverse relationship between metabolic rate and blood cholesterol level. We are forced to the somewhat unexpected conclusion that the single plasma cholesterol determination gives no aid in making a diagnosis of thyroid disturbance in a given individual.

In passing over the material, we selected at random 20 patients of the group who had obesity as an outstanding physical finding.

TABLE VII

Cholesterol Values in Patients with Varying Degrees of Obesity

Weight	Plasma Cholesterol
184	188 mg.
198	138 mg.
179	219 mg.
165	240 mg.
210	150 mg.
194	194 mg.
153	118 mg.
185	168 mg.
182	266 mg.
166	128 mg.
170	154 mg.
155	198 mg.
173	120 mg.
300	136 mg.
183	130 mg.
192	133 mg.
212	164 mg.
159	140 mg.
175	200 mg.
160	130 mg.

There is no correlation here to attract our attention. Of the entire group of patients considered, only four had a positive blood Wassermann. The cholesterol values were 182, 158, 130, and 166 mg., respectively. A study of blood pressure with a view to the circulating cholesterol gave just as great a distribution of figures over the wide range as was found in the control series.

DISCUSSION

As early as 1922, Epstein and Lande [5] called attention to an inverse relationship between blood cholesterol values and metabolic rates. Gardner and Gainsborough [6] also noted such a relationship and refrained from attaching great significance to it because of the many exceptions to the findings in a few cases.

Hurxthal [7, 8, 9, 10, 11] and co-workers have found cholesteremia in myxedema consistently, and a less regular but significantly low blood cholesterol in thyrotoxicosis. They have observed more than 500 patients in reaching this conclusion and feel that "cholesteremia in the absence of its few other common causes, points more specifically to thyroid deficiency than does the finding of a low basal metabolism." Goldbloom and Gottlieb,[12] in 1927, and Bronstein,[13] in 1933, found an increase of blood cholesterol in cretins.

On the other hand, Levy,[14] in a group of 10 patients with exophthalmic goiter, found six with a blood cholesterol value of more than 230 mg.

Gilligan [15] and collaborators observed cholesteremia in patients with low metabolisms and no clinical evidence of hypothyroidism. After thyroidectomy, these patients failed to keep a constant relationship between the basal metabolism and the blood cholesterol level.

Luden [16] found the blood cholesterol in 35 cases of exophthalmic goiter to be within normal range, and Wade [17] reported slightly increased values of blood cholesterol in patients with toxic goiter. Castex and Schteingart [18] found no relationship between the basal metabolic rate and blood cholesterol values. In this connection it is of interest that Cutting [19] and his coworkers, as well as Grant and Schube,[20] obtained no correlation whatever between blood cholesterol and metabolic elevations induced by dinitrophenol.

Several pertinent observations on blood cholesterol furnish some explanation to the finding of inconstant values in this or in other such series. Barreda [21] evaluated the cholesterol tolerance test of Thannhauser and Burger in which five grams of cholesterol in olive oil are taken by mouth and the blood level determined four and 24 hours later. He obtained variable results in normal and diseased adults in that the blood cholesterol level often was lower four hours after ingesting cholesterol than before. Yet Wendt [22] finds that the ingestion of olive oil alone increases the phosphatid and cholesterol level four hours after ingestion. Gardner and Gainsborough [23] and Bloor,[24] in reference to widely discrepant normal values, emphasize the taking of fasting blood samples. These authors are agreed that the level of the cholesterol content of human plasma, taken while fasting, can be raised or lowered by sufficiently prolonged feeding with diets of high or low sterol content. They are not agreed on the effect of a single meal on blood cholesterol (alimentary hypercholesterolemia) but the evidence is possibly more in favor of some degree of relationship generally between the amount of sterol ingested and the cholesterol level of the plasma during its immediate digestion.[24, 25, 26]

Among published "normal" blood total cholesterol figures there are noteworthy variations. Bloor [27] found the plasma values for men to be from 170 mg. to 311 mg., with an average value of 220 mg., and the values for women to be from 210 mg. to 260 mg., with an average value of 240 mg. Most authors make no distinction according to sex. The normal, according to Klinert and Widal (quoted by Campbell [28]), is 180 mg., while Campbell [28] suggests the range of 150 mg. to 200 mg. Milbradt,[29] comparing his own use of the Tschugaew reaction with other methods for cholesterol determination, finds the normal values extending from 103.6 mg. (Autenrieth) to 176.3 mg. Gardner and Gainsborough [30, 23] find the normal fasting variance to be 131 mg. to 293 mg., with an average value of 200 mg. Hunt,[31] with Bloor's [1] method, found a variance of from 118 mg. to 272 mg., with an average of 177 mg. cholesterol in normal blood. Denis [32] had a range of 167 mg. to 255 mg., with an average of 220 mg. in his series of normal subjects. Epstein and Lande,[5] using the Bloor [1] method soon after its publication, had normal values extending from 160 mg. to 200 mg., with most

of their values near the upper figure. Boyd [4] found the normal total plasma cholesterol to be 162 mg. as determined by his oxidative procedure.

That one or more factors controlling the level of cholesterol in the normal blood plasma are beyond our present knowledge seems obvious. The variations in the majority of normal series are too great to allow unqualified interpretation of values in disease states. There is a concurrence in this view in the expressed conclusions of several workers thoroughly acquainted with blood cholesterol values. Gardner and Gainsborough [6] state that "in normal human plasma the variations of cholesterol content are so considerable that an average figure for the normal plasma cholesterol is devoid of meaning unless the normal limits of variation are taken into account." Hunt [21] and Bloor [24] have expressed similar opinions.

The action of a protein-precipitant is necessary if any fat solvent is to remove satisfactorily the cholesterol from plasma. This suggests the power of protein to retain cholesterol. The marked insolubility of cholesterol in water would make necessary such a function of protein or some other circulating constituent. Gardner and Gainsborough [33] suggest that changes in the globulin-albumin ratio of blood may be related to the variations in sterol content of plasma under both normal and abnormal physiological conditions in man.

In seeking to understand disagreements between our findings and those indicating a more constant relationship between cholesterol metabolism and thyroid function a word might be said concerning the method. The author [34] has used various blood cholesterol methods for several years and is acutely aware of their limitations. Periodically the standard solutions were checked. The time element and temperature of the solution affect appreciably the depth of blue. Bloch,[35] in 1933, studied each step in the estimation of cholesterol by the Liebermann-Burchard color reaction, using the time of the maximum reaction, temperature, light, solvent, concentration of cholesterol, quantity of sulphuric acid, and quantity of acetic anhydride as variables in apparently well-controlled observations. He found that the color developed in 15 minutes by the Liebermann-Burchard reaction is due to only two-thirds of the cholesterol present but finds that this is constant. The optimum conditions which he determined are embodied in the Sackett [2] procedure as used in these analyses.

Ninety per cent of the estimations were made by the author. The remaining analyses were made by a well-qualified senior medical student. It was found that an error of 5 to 8 per cent might appear in trials of the method made by using various known solutions of cholesterol and by adding varying quantities to blood filtrates. All standard and unknown solutions were prepared in duplicate. The type of patient from whom blood was taken was rarely known to the author at the time of the estimation. Occasionally the two standards, for an unexplained reason, failed to check properly. In such instances the entire analysis of a fresh portion of the blood plasma was repeated. An electrically illuminated Klett colorimeter was used

in a location protected from the glare of extraneous light. We feel that there can be no question but what the great variations are due to an actual variation in the amount of blood sterol compounds reacting with acetic anhydride and sulphuric acid in chloroform solution.

Evidence is accumulating that body sterols are effective substances in minute amounts; that many closely related forms are to be found with slightly different degrees of saturation, or positions of chemical groups in the sterol nucleus, and with greatly different biological influences.[26, 36] It is now apparent that a close chemical relationship exists between cholesterol and crystalline vitamin D, estrogenic and male sex hormones, cardiac glucosides, carcinogenic hydrocarbons, bile acids, etc.[36, 37] Then may not our plasma "cholesterol" readings be a titer of numerous circulating entities, each present in small and varying amounts in health and disease? Is it not likely that the sterol causing the cholesterol figure in plasma from a patient with carcinoma is entirely different from that compound producing the greater part of the color in an estimation from the plasma of a patient with myxedema?

The possibility of a geographic or climatic cause for the behavior of blood cholesterol cannot be dismissed since it has been difficult for workers to agree upon the normal figures for blood cholesterol using the same method in different parts of this country and in other countries.

Conclusions

1. The figures for fasting blood plasma cholesterol in 52 normal adults, by a reasonably well controlled laboratory procedure, cover a wide range. The lowest finding was 150 mg. and the highest 228 mg., with an average of 193 mg.

2. In 145 patients having the plasma cholesterol and metabolic rate determined concomitantly there was no suggestion of correlation between the two.

3. In a series of 45 of the above patients presenting a metabolic rate above the arbitrarily chosen figure of + 10, the sought-for correlation was not apparent. In 16 individuals presenting the undoubted clinical picture of thyrotoxicosis, the cholesterol variation was not consistent for the group.

4. In a series of 42 patients of the total group a metabolic rate of less than — 10 was found. Of these, 19 patients had well-defined evidence of a hypothyroid state. Here, too, there was no tendency for the plasma cholesterol value to reflect the condition of the patient.

5. The factors affecting the circulating cholesterol are too numerous for a single estimation to be of great significance in the diagnosis of disturbance of the thyroid function. That thyroid disease is accompanied by cholesterol changes is not to be doubted, and plasma cholesterol estimations may prove of aid in following the progress of an individual patient under treatment provided such estimations are made frequently.

In this study the author had the excellent coöperation of Dr. E. M. Dunstan, Director of Clinics and Medical Director of Baylor University Hospital, Dr. C. Frank Brown, Chief of the Metabolism Clinic of Baylor University Medical Dispensary, as well as numerous senior students in collecting and preserving specimens of blood plasma.

BIBLIOGRAPHY

1. Bloor, W. R.: Cholesterol in blood, Jr. Biol. Chem., 1916, xxiv, 227–231.
2. Sackett, G.: Modification of Bloor's method for determination of cholesterol in whole blood or blood serum, Jr. Biol. Chem., 1925, lxiv, 203–205.
3. Bloor, W. R., and Knudson, A.: Determination of cholesterol in small amounts of blood, Jr. Biol. Chem., 1916, xxvii, 107–112.
4. Boyd, E. M.: A differential lipid analysis of blood plasma, Jr. Biol. Chem., 1933, ci, 323–336, 623–633.
5. Epstein, A. A., and Lande, H.: Studies on blood lipoids, the relation of cholesterol and protein deficiency to basal metabolism, Arch. Int. Med., 1922, xxx, 563–577.
6. Gardner, J. A., and Gainsborough, H.: The relation of plasma cholesterol to basal metabolism, Brit. Med. Jr., 1928, ii, 935–937.
7. Mason, R. L., Hurst, H. M., and Hurxthal, L. M.: Blood cholesterol values in hyperthyroidism and hypothyroidism: their significance, New England Jr. Med., 1930, cciii, 1273–1278.
8. Hurxthal, L. M.: Blood cholesterol in thyroid disease; effect of treatment, Arch. Int. Med., 1933, lii, 86–95.
9. Hurxthal, L. M.: Blood cholesterol in thyroid disease, Arch. Int. Med., 1933, li, 22–32.
10. Hurxthal, L. M.: Blood cholesterol and thyroid disease; myxedema and hypercholesterolemia, Arch. Int. Med., 1934, liii, 762–781.
11. Hurxthal, L. M.: Blood cholesterol and hypometabolism, etc., Arch. Int. Med., 1934, liii, 825–831.
12. Goldbloom, A., and Gottlieb, R.: The cholesterol content of the blood of infants and children, Canad. Med. Assoc. Jr., 1927, xvii, 1333–1336.
13. Bronstein, I. P.: Studies in cretinism and hypothyroidism in childhood. I. Blood cholesterol, Jr. Am. Med. Assoc., 1933, c, 1661–1663.
14. Levy, M.: Les variations du cholestérol chez les basedowiens traités par la radiothérapia, Bull. et mém. Soc. méd. d. hôp. de Paris, 1931, xlvii, 1844–1846.
15. Gilligan, D. R., Volk, M. C., Davis, D., and Blumgart, H. L.: Total ablation of normal thyroid; relationship between serum cholesterol values, etc., Arch. Int. Med., 1934, liv, 746–757.
16. Luden, G.: Blood cholesterol in malignant disease and the effect of radium on the blood cholesterol, Collected Papers of the Mayo Clinic, 1918, x, 481–487.
17. Wade, P. A.: Clinical and experimental studies on calcium and cholesterol in relation to thyroid-parathyroid apparatus, Am. Jr. Med. Sci., 1929, clxxvii, 790–816.
18. Castex, M. R., and Schteingart, M.: La colesterinemia y la calcemia en los estados tiroideos; sus relaciones con el metabolismo basal, Soc. Rev. de Med. Int. (Buenos Aires), 1925, i, 514–525.
19. Cutting, W. C., Ryland, D. A., and Tainter, M. L.: Relationship between cholesterol and increased metabolism from dinitrophenol and thyroid, Jr. Clin. Invest., 1934, xiii, 547–552.
20. Grant, L. F., and Schube, P. G.: Effect of alpha dinitrophenol 1–2–4 on man, Jr. Lab. and Clin. Med., 1934, xx, 56–61.
21. Barreda, P.: Über den diagnostischen Wert von Blutcholesterinbestimmungen nach peroraler Cholesterinbelastung, Klin. Wchnschr., 1934, xiii, 290–292.
22. Wendt, H.: Über das Verhalten der Phosphatide und des Cholesterins in Gesamtblut Plasma und Erythrocyten des gesunden Menschen nach Olivenölbelastung mit und ohne vorherige Phosphat darreichung, Biochem. Ztschr., 1932, ccl, 212–219.

23. GARDNER, J. A., and GAINSBOROUGH, H.: Studies on the cholesterol content of normal human plasma, on the so-called alimentary hypercholesterolemia, Biochem. Jr., 1928, xxii, 1048–1056.
24. BLOOR, W. R.: Diet and the blood lipids, Jr. Biol. Chem., 1932, xcv, 633–644.
25. MAN, E. B., and GILDEA, E. F.: The effect of the ingestion of a large amount of fat and of a balanced meal on blood lipids of normal man, Jr. Biol. Chem., 1932–33, xcix, 61–69.
26. MCCLURE, C. W., and HUNTSINGER, M. E.: The influence on blood lipids of single foodstuffs, Jr. Biol. Chem., 1928, lxxvi, 1–18.
27. BLOOR, W. R.: The distribution of the lipoids (fat) in human blood, Jr. Biol. Chem., 1916, xxv, 577–599.
28. CAMPBELL, J. M. H.: Cholesterol in health and disease, Quart. Jr. Med., 1925, xviii, 393–422.
29. MILBRADT, W.: Zur Bestimmung von Cholesterin und Phosphatiden in kleinsten Gewebs- und Blutmengen, Ztschr. f. physiol. Chem., 1933, ccxvi, 181–188.
30. GARDNER, J. A., and GAINSBOROUGH, H.: Studies on the cholesterol content of normal human plasma, Biochem. Jr., 1929, xxi, 130–140.
31. HUNT, H. M.: Cholesterol in the blood of diabetic patients treated at the New England Deaconess Hospital, New England Jr. Med., 1929, cci, 659–667.
32. DENIS, W.: Cholesterol in human blood under pathological conditions, Jr. Biol. Chem., 1917, xxix, 93–110.
33. GARDNER, J. A., and GAINSBOROUGH, H.: Studies on the cholesterol content of normal human plasma; the attraction of the proteins of plasma for sterols, Biochem. Jr., 1927, xxi, 141–147.
34. GRAY, H., and MCGEE, L. C.: Cholesterol content of blood in epilepsy and in feeblemindedness, Arch. Neurol. and Psychiat., 1932, xxviii, 357–369.
35. BLOCH, A.: Das Cholesterin bei der Liebermann-Burchardschen Farbreaktion, Biochem. Ztschr., 1933, cclvii, 171–179.
36. BLOOR, W. R.: Fat metabolism, Ann. Rev. Biochem., 1933, ii, 147–164.
37. ROSENHEIM, O., and KING, H.: Chemistry of the sterols, bile acids and other cyclic constituents of natural fats and oils, Ann. Rev. Biochem., 1934, iii, 87–110.

THE USE OF HELIUM IN THE TREATMENT OF ASTHMA AND OBSTRUCTIVE LESIONS IN THE LARYNX AND TRACHEA *

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INTRODUCTION

THE proposal of helium as a new therapeutic gas was based on the conception that its decreased specific gravity in relation to nitrogen would make a helium-oxygen mixture easier to breathe than a comparable nitrogen-oxygen mixture, such as occurs in air.[1] The molecular weight of helium being 4, and that of nitrogen 28, the substitution of 80 per cent helium for 80 per cent nitrogen, with the oxygen concentration 20 per cent, would provide a respirable gas mixture which would have 33 per cent of the density of air (table 1). Utilizing the physical formula F equals MA, where F

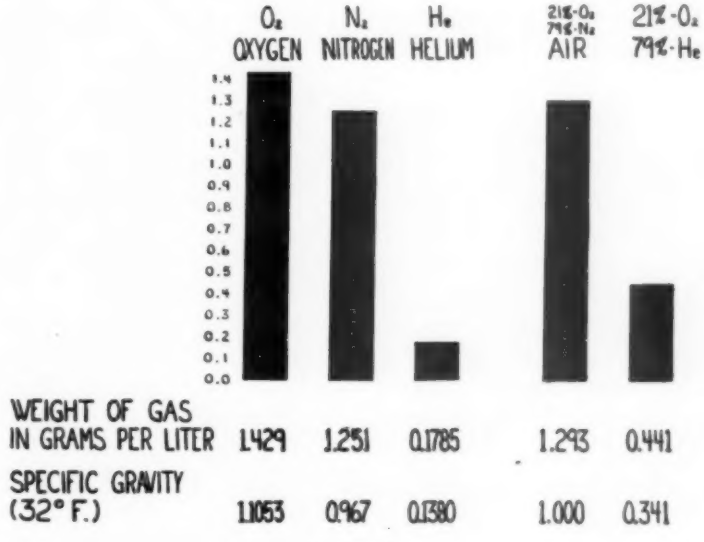

TABLE 1

Comparative weight of the respirable gases per liter.

is Force, M is Mass and A is Acceleration, it may be said in general that the force necessary to transport a gas, other things being equal, is propor-

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.
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† The author wishes to acknowledge assistance rendered to him by the United States Public Health Service, Bureau of Medicine and Surgery, United States Navy; The Linde Air Products Company, and the Helium Company, and to express his appreciation for their aid.

‡ With the technical assistance of Morris Eckman, B. S.

tional to the density of the gas, and that in the case of an 80 per cent helium-20 per cent oxygen mixture, the force required would be one-third that necessary for movement of an 80 per cent nitrogen-20 per cent oxygen mixture. When passage of a gas through very fine orifices is considered, the rate of diffusion is proportional to the square root of the density; under these circumstances, the pressure required for this type of gas movement for an 80 per cent helium-20 per cent oxygen mixture would be approximately one-half that required for air.[2]

Wherever there is obstruction to the movement of air in the respiratory tract, an increased pressure is necessary to transport air to and from the lungs. In long-continued or severe obstruction, the increased back-pressure causes distention of the pulmonary alveoli and impairment in their function. The substitution of helium for nitrogen provides a respirable mixture which may be breathed with a pressure theoretically one-half to one-third that used for air. In previous reports [1, 2] it was shown that the force required for human subjects to breathe through narrow orifices was 35 to 50 per cent less when helium-oxygen mixtures were inhaled instead of air. This saving in respiratory effort has been made use of in patients with severe asthma and obstructive lesions in the larynx and trachea.

Historical

Helium was discovered in the sun in 1868 by Jannsen and Lockyer [3] by means of the spectroscope. Its existence on earth was demonstrated by Ramsay [4] who obtained it from the mineral cleavite. It was later found to be a constituent of the atmosphere to the extent of one part in 200,000. Recently, it has been found to occur in certain natural gases. It has been used in dirigibles because of its buoyancy, having displaced hydrogen because it is free from explosive possibilities. In 1923, a patent was registered in the United States Patent Office by Charles Cooke [5] for the use of helium with oxygen for divers, based on the fact that helium has a coefficient of solubility approximately half that of nitrogen, and because it is twice as diffusible. Sayers and Yant [6] in 1926 decompressed animals from 10 atmospheres of helium-oxygen mixtures in from one-third to one-fourth the time necessary for nitrogen-oxygen mixtures and found no toxic effects from the use of helium under high pressures for short periods.*

In a series of papers Hershey [7] reported that exclusion of rare gases from the atmosphere was not compatible with life, using small animals such as mice for experimental subjects. The author,[8] during the past two years, carefully tested this hypothesis and found that animals lived apparently uninfluenced in atmospheres in which the rare gases were excluded for periods as long as 42 days. That helium was not itself harmful was next tested.

* Elihu Thompson (Science, 1927, lxv, 36) called attention to correspondence with the U. S. Bureau of Mines in which he suggested the use of helium for divers in 1919, the conception having apparently arisen out of earlier experiments with hydrogen and oxygen performed in 1873.

A series of animals (mice) were kept in completely sealed chambers in which there was 79 per cent helium and 21 per cent oxygen. The chamber was cleaned twice a week; the technic of maintaining a constant percentage of the mixture has been described previously.[8] The mice seemed uninfluenced by the substitution of helium for nitrogen for periods of two months, confirming previous evidence of its biologic inertness. Helium was then proposed as a therapeutic gas,[1] because its physical property of possessing the smallest specific gravity of any of the elements except hydrogen suggested that it could be moved more easily to and from the lungs in conditions where obstructive dyspnea was present. The highly explosive nature of hydrogen when mixed with oxygen excludes its clinical use.

Methods

The administration of helium presents certain hazards that are more difficult to overcome than those encountered in the effective therapeutic use of oxygen. It is well known that oxygen therapy for years was employed in such small concentrations as to be of little or no value. The importance of knowing the concentration of oxygen inhaled by the patient has become generally recognized wherever high standards of medical practice are present; there are still to be found, however, instances of oxygen tent therapy in which the concentration of oxygen administered is not known. The patient may or may not be benefited under these haphazard practices but is not apt to be injured. In the use of helium mixed with oxygen, the danger of an inert gas displacing too much oxygen is constantly present, since an excess of helium will produce asphyxia. Careful oversight is also necessary to accomplish a rigid exclusion of nitrogen, for the beneficial effects of the inhalation of a lighter-than-air gas are lost when an inward leak of air enters the therapeutic atmosphere. Finally, the helium itself should be tested by an accurate helium analyzer to make sure that it is 97 to 99 per cent pure.

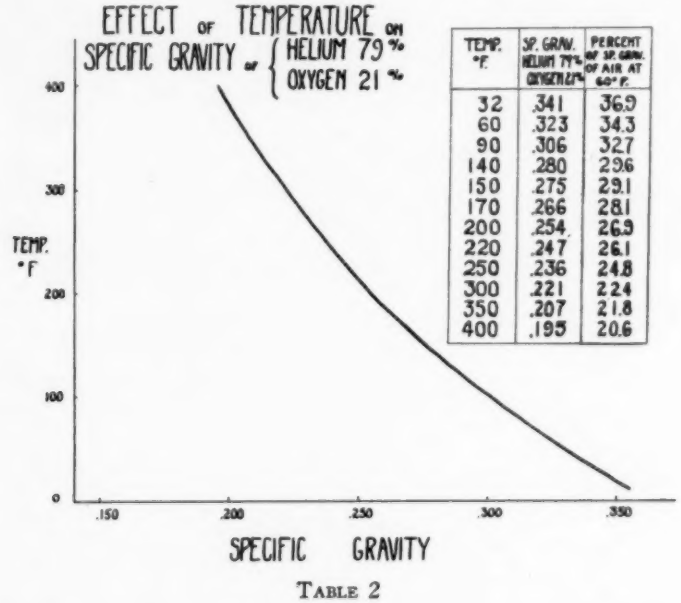
The present high cost of helium commercially makes it expedient to use it as economically as possible.* The apparatus employed for oxygen administration cannot be simply turned over for administration of helium and oxygen. A leak in an oxygen tent, for example, will create a loss of helium that will speedily destroy the value of the procedure. The greater diffusivity of helium over oxygen or air makes it necessary to employ special balloon material to prevent loss by diffusion through the tent fabric. Several methods have been developed.

For relatively short periods of administration, such as one hour, a mask or mouthpiece apparatus has been used. A light rubber mask which fits tightly yet reasonably comfortably to the face is equipped with two one-inch outlets. One outlet is connected to the outside air by a rubber hose which

*Helium may be obtained from the Helium Company, Louisville, Kentucky. The Government has a large plant at Amarillo, Texas, which serves the Navy, the Army and other Government departments, but does not sell helium.

has an expiratory flutter valve at the terminal end. The other outlet is connected to an inspiratory flutter valve and then to a two-way metal valve by one-inch brass or mica tubing. The other end of the three-way valve is in turn connected to a Douglas bag, into which the gas mixture is admitted. A heater may be inserted three to four inches from the mask. When a heater is employed, a mouthpiece is used to inhale the heated helium oxygen mixture, a thermometer being inserted just in front of the mouthpiece. The metal parts of the apparatus are insulated.

The purpose of using heated helium-oxygen mixtures is to decrease still further the density of the mixtures. Dry air between 200 and 250° F. has been employed in some cases. In the accompanying table (table 1)



TEMP. °F.	SP. GRAV. HELIUM 79% OXYGEN 21%	PERCENT OF SP. GRAV. OF AIR AT 60° F.
32	.341	36.9
60	.323	34.3
90	.306	32.7
140	.280	29.6
150	.275	29.1
170	.266	28.1
200	.254	26.9
220	.247	26.1
250	.236	24.8
300	.221	22.4
350	.207	21.8
400	.195	20.6

TABLE 2

the effect of increasing temperatures on the specific gravity of a gas is shown. The gas during respiration is gradually deprived of most of its heat and becomes saturated. However, the fact that the expired air may be 10 degrees higher than expired unheated air [9] indicates that the inhaled heated gas is considerably less dense when it is passing through the bronchi. Helium-oxygen mixtures at room temperature have been used in most instances.

Before treatment is begun, the Douglas bag is filled with helium and oxygen delivered from separate tanks through suitably calibrated gauges to make a mixture of 15 to 20 per cent oxygen and 85 to 80 per cent helium. As a check on the concentration finally attained, it is helpful to test the concentration of the combined gas as it enters the bag, or after it is filled. The inlet of the gas mixture is now changed so that it is run into the metal

tube that connects with the mask or mouthpiece, which is then attached to the patient. In many instances, 15 liters of helium and 3 liters of oxygen are thus admitted. As treatment is begun the two-way valve is turned so that the mixture from the Douglas bag is partly inhaled with the gas entering near the mouthpiece. When the bag is emptied, the patient is disconnected from the apparatus, the two-way valve closed so that the Douglas bag may again be filled, and the treatment begun again. The reason for switching the inlet of oxygen and helium from the bag reservoir to the mouthpiece connection is that a slight positive pressure is thereby developed which facilitates the inlet of the gas into the lungs.*

Experiments are in progress to develop a satisfactory method of re-using helium, by adding to a closed system the oxygen consumed by the patient. If valves are employed to circulate the gas through soda-lime, a positive pressure must be maintained to facilitate inspiration, since the patient with asthma finds it especially burdensome to develop additional inspiratory negative pressure to overcome the resistance in the tubing. A slight positive pressure in the system overcomes this resistance, which is then present during expiration. However, a slight increase in resistance to expiration is not uncomfortable and at times actually appears to facilitate the egress of the gas, perhaps by preventing further collapse of the bronchiole by high expiratory pressures. A motor-blower unit may be used to circulate the mixture through the system, provided also a slight positive

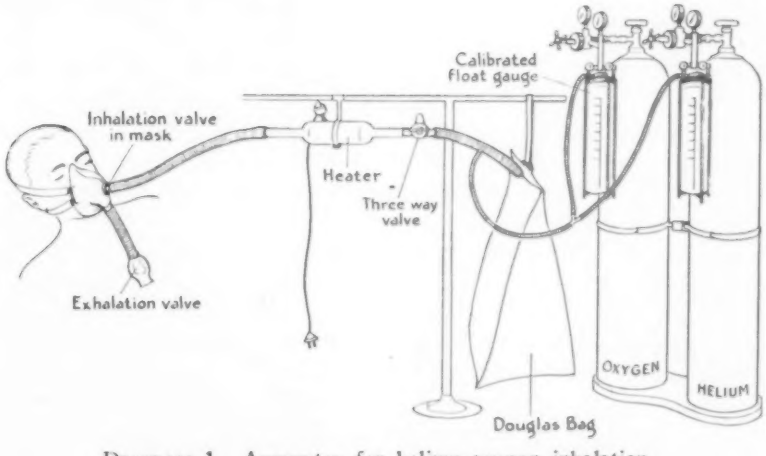


DIAGRAM 1. Apparatus for helium-oxygen inhalation.

* The inspiratory flutter valve should be slit open ¾ inch further to decrease resistance during periods when large tidal volumes are inhaled.

The complete apparatus may be obtained from the Oxygen Therapy Service Company, New York.

The mask and the helium analyzer are made by the Mine Rescue Appliance Company, Pittsburgh, Pa.

The oxygen regulator is made by the Linde Air Products Company, New York.

The Forreger Company, New York, manufactures a calibrated water bottle.

The heater is supplied by the Gruenberg Electric Company.

The Helium Company is preparing mixtures of 20 per cent oxygen and 80 per cent helium which will simplify the administration of the gas.

pressure is maintained. (Diagram 2.) A method of increasing pressure during inspiration and decreasing it during expiration, which will be synchronous with the patient's respiration, is being developed. In any of the methods employed to re-use the helium, the system must first be thoroughly

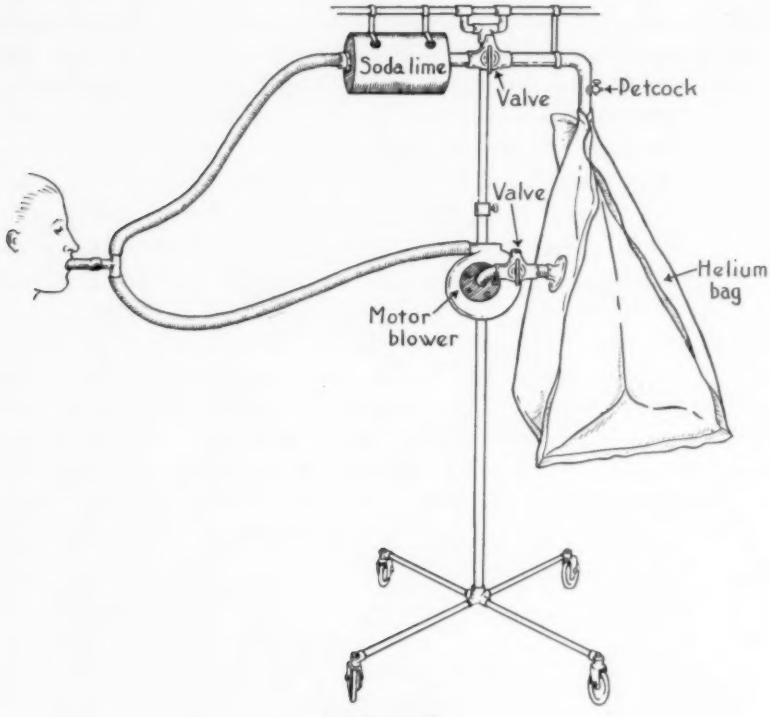


DIAGRAM 2

Helium rebreathing apparatus utilizing increased pressures.

flushed with the gas mixture to remove all traces of nitrogen and a by-pass valve inserted by which the patient can breathe out the nitrogen of his residual air. Oxygen is then admitted at a rate which corresponds to the patient's estimated basal metabolism. Repeated checks of the oxygen concentration are necessary to determine whether the inflow of oxygen is adequate to maintain the desired oxygen concentration. Tests of the helium concentration reveal the presence or absence of inward air leaks.

The oxygen tent has been modified to adapt it to the administration of helium with oxygen. The cooling, drying and ventilating are accomplished, as originally recommended, by direct passage of the atmosphere over chunks of ice.[10] The motor-blower unit must be leak-tight to helium. The canopy which encloses the patient is made out of special helium-proof balloon fabric. The material should be in one piece with an opening which makes a closure around the neck, or, particularly in infants, which takes in the entire body. This opening is closed with zippers and the surrounding

cloth folded over several times and clamped. Similar openings are present for administration of food and medicine. In both the adult and infant tents, a sleeve protrudes into the tent with a glove at the end, closed off from the inside atmosphere. The nurse may thus assist the patient without creating a leak. When treatment is commenced, in the tent used for adults, a bag is inflated within the tent, with the patient inside, with pure helium, while the remainder of the tent atmosphere is flushed out with a vigorous stream of pure oxygen. Air or nitrogen is thus reduced to a minimum. The bag is then opened within the tent. Adjustment of the desired concentration of helium and oxygen is accomplished by admission of these gases through calibrated gauges. If the canopy is built so that only the head of the patient is enclosed and contact is made around the neck, considerable saving of helium is effected.*

A helium testing apparatus has been developed by the Mine Rescue Appliance Company, based on the different diffusion propensities of air and helium. The helium concentration may be read off a dial within an accuracy of 0.5 per cent, in half a minute after the gas sample has been admitted into the diffusion chamber. A simpler, less expensive but less accurate apparatus may be constructed by calibrating the variable depression made on a water manometer by light and dense gases. If a constriction to the outflow of gas is produced, a considerable difference in water level will occur when a constant volume of air is delivered as compared to mixtures containing variable percentages of helium.

Since it is of obvious importance that the oxygen supply should never be interrupted, whatever method of administering helium and oxygen is used, two precautions have been adopted. The oxygen and helium gases are joined by a Y-tube immediately after their delivery from the gauge and passed thence into the tent by a *single* hose. The oxygen tank is connected by an arrangement developed by the Linde Air Products Company to a reserve tank which automatically delivers oxygen should anything happen to the one in use, such as the tank becoming empty or the valve inadvertently turned lower than the prescribed flow. The principle is simply that the reserve tank is set at a pressure just slightly lower than that at which oxygen is being delivered, and would therefore begin to function if the pressure in the first tank was for any reason decreased. An additional safeguard is an alarm which goes off when the oxygen flow stops.

The precautions enumerated and the determination of both oxygen and helium concentrations are necessary both for the effective use of this gas mixture as well as to safeguard the patient.†

* The adult tent was built by the Oxygen Therapy Service Company, New York, and the infant model by Mr. John Emerson, Boston, Mass.

† The effect of helium on the voice is characteristic and is a rough index of the presence of a high helium concentration. A high, quavering note is produced, resembling that of an old man or old woman. The lighter gas decreases the chest resonance. Inhalation of argon-oxygen mixtures has given the voice an opposite quality, increasing chest resonance because of its greater density.

For those who plan to use helium therapeutically a few additional words on special problems involved in its administration may be helpful, especially since we are employing at the present writing methods which are being gradually improved.

In the simplest form of administration, the helium-oxygen mixture is inhaled partly from a Douglas bag and partly from the stream of the gas which enters near the mouthpiece. The importance of having the inhaled mixture enter near the mouthpiece instead of from the bag alone is that a slight increased pressure is thereby obtained which noticeably increases the comfort of the patient. The bag should be filled with the mixture before treatment is begun; from then on the desired flow, for example, 16 liters per minute of helium and 4 liters oxygen, is transferred to entrance near the mouthpiece. This flow would be necessary for only very high pulmonary ventilations; half as much would be used for low pulmonary ventilations. The exhaled atmosphere is wasted, passing into the air through the expiratory flutter valve.

For economic reasons it is highly desirable to re-use helium. A simple closed system in which the atmosphere would be blown through soda-lime presented certain difficulties. The first one was that leakage in the motor blower unit contaminated the atmosphere with nitrogen and lost helium more rapidly than oxygen because of its decreased density. It was found that if a pressure of 3 to 14 cm. of water was maintained in the system, the leaks would be outward and would therefore prevent entrance of nitrogen. This was done by insertion of a variable resistance in the tubing through which the exhaled air was passed. This increased pressure was found to be of decided value in increasing the velocity of the helium-oxygen mixture during inspiration without causing additional discomfort during expiration. (The reasons for this may be gathered from the body of this article and a forthcoming study on animal experiments.) Since it is known that the velocity of a gas is proportional to the square root of the increase in pressure, it became obvious that we could gain more by raising the pressure of the inhaled gas than we could by lightening its density through increasing its temperature, and we therefore have concentrated our attention on this phase of technic more recently.

By employing a Sturtevant motor-blower unit, the leakage in this closed system is slight; 4 liters of helium and 1 liter of oxygen per minute more than suffice to maintain the original atmosphere. Progress is being made in further reducing the leakage. In this apparatus, when the patient begins breathing through the mouthpiece, he first inhales air through the small valve mechanism to which the mouthpiece is attached. The Douglas bag is filled with the desired helium-oxygen mixture, usually 20 per cent oxygen, 80 per cent helium (at times 15 to 19 per cent oxygen, the remainder helium). A valve connected with the exhalation tubing is turned so that the patient's expired air goes into the atmosphere instead of into the closed system, in order that the 2 liters or more of the nitrogen of his residual air does not contaminate the helium-oxygen mixture being built up in the bag. The valve at the mouthpiece is next turned so that the patient inhales the helium-oxygen mixture instead of air. After he has taken 8 breaths, he has quite well washed the nitrogen out of his lungs, and the valve referred to on the exhalation tubing side may now be turned so that he breathes into the closed system and the helium is re-used. The motor-blower unit is now turned on adding the increased pressure to inspiration. The reason that the turning on of the motor-blower unit has been delayed to this time is to prevent the large loss of helium which would otherwise have taken place when the patient was discharging the nitrogen of his residual air into the atmosphere.

When the bag has been filled, a flow of 4 liters of helium and 1 of oxygen maintains the helium concentration approximately constant. The oxygen consumption of the patient, 200 to 400 c.c., may have to be compensated for by a very slight increase in the oxygen admitted, thus 1.2 instead of 1.0 c.c. As we usually employ 17 per cent oxygen, the relatively small oxygen consumption by the patient makes little difference at the above flow; for after a little while the bag gets too full and a valve in the cir-

cuit past the bag must be opened and the gas mixture allowed to run into the air until the bag is somewhat reduced in size.

If an absolutely leak-tight motor-blower unit were found, then it would be necessary merely to run in 200 to 400 c.c. of oxygen, depending on the oxygen consumption of the patient. It is obviously important to test the oxygen concentration of the gas entering the bag, which can be easily done in a minute by withdrawing a sample from a T-tube inserted in the rubber tubing which leads to the bag. The oxygen concentration in the closed system itself should also be tested to guard against leaks. Our practice is also to test the helium concentration by a densiometer, which reassures the operator of his technic in excluding nitrogen. It is essential to test the oxygen concentration to prevent undue accumulation of helium to asphyxial proportions. For that reason, the responsibility of administering this gas must rest with a physician; a technician may be employed to administer the gas under the physician's direction and responsibility, but it is not justifiable for a physician who does not comprehend the technic to request helium therapy from a purely technical service. The danger of death from asphyxiation is too real to be put under the control and management of technicians. With oxygen therapy the situation is obviously different inasmuch as no risk from asphyxia is present.

The author is at the moment experimenting with the Russ-Beach pump, which is air-tight, and with the Roots-Connersville blower. They possess the additional advantage of being capable of delivering the atmospheres at higher pressures, such as 10 to 13 cm. of water, which enormously facilitate the entrance of the gas during inspiration but are high for expiration. An apparatus has been used in which the technician or nurse operates manually a valve by which the pressure is removed during exhalation and introduced during inspiration. An attempt is being made to accomplish this electrically by use of a photoelectric cell inserted near the patient's mouth. A small vane which moves toward the mouth during inspiration and away from the mouth during expiration interrupts a light from a photoelectric cell. The practicability of this latter apparatus has yet to be demonstrated; it is mentioned at this time for those individuals who actually plan to use helium.

The special importance of utilizing increased pressures during inspiration is to diminish the intrathoracic negative pressure which is high in obstructive dyspnea. In animal experiments the author has shown that edema of the lungs may occur in three hours, with circulatory failure, after continuous breathing through a resistance. The high intrapleural pressure not only acts like cupping the lungs but also sucks blood in the right heart and tends to prevent it from leaving the lungs, with resultant inadequate filling of the left ventricle. It has been shown that attacks of cardiac asthma are associated with a sudden increase in the volume of blood in the lungs (Weiss, S. and Robb, G. P.: Jr. Am. Med. Assoc., 1933, c, 1841). The administration of helium and oxygen under pressure not only facilitates pulmonary ventilation but also lessens intrathoracic pressure, decreasing the accumulation of blood in the lungs, tending to prevent or to ameliorate edema of the lungs and circulatory failure.

Results

A. Asthma. The rôle of helium in the treatment of asthma will be presented by reciting the histories of four patients in whom its therapeutic value is manifested and by illustrating through graphic records its effect on various phases of pulmonary ventilation.

The graphs in Case 1 were obtained by the patient breathing through a mouthpiece into a basal metabolism apparatus in which the CO_2 was removed either by the patient's respirations through soda-lime or by means of a motor. Low and high speed drums were used to record the qualitative

as well as the quantitative changes in pulmonary ventilation. In addition, a measurement was taken which will be referred to as the pressure in the pulmonary air-way. The tube that leads off from the patient's mouth is tapped by a hard rubber hose that is in turn connected to a water manometer. As the patient breathes, especially when there is resistance external to the site where the breathing tube is tapped or when rapid forceful respirations are present, the pressure required to move the air in the respiratory system is communicated to the water manometer. The excursions of the water level are recorded on a moving drum by means of a delicate float which rides in the water of the distal arm of the manometer and which has attached to it a fine pen. The pressure readings thus obtained represent the pressure against which the respiratory musculature works and become thus an indirect index of respiratory effort. When the pulmonary air-way is entirely unobstructed and when respiration is proceeding slowly and quietly, there are recorded only very slight pressure differences. However, when rapid movement of air becomes necessary and particularly when a hindrance to the free passage of air develops in any part of the respiratory tract, the pressure in the pulmonary air-way is markedly increased and it is therefore under these circumstances that the decrease in the effort necessary to move a relatively light helium-oxygen gas becomes of clinical importance.

Case Reports

Case 1. Male, age 26 years. Patient entered the Hospital on his sixth admission complaining of severe continuous asthma of 48 hours' duration. Attacks of asthma began two years ago. Since then, he had been admitted five times for severe asthma, complicated by either sinusitis, bronchitis or bronchopneumonia. Allergic skin tests were negative. Treatment in addition to rest was mainly directed to his sinuses, although radical procedures were not undertaken. He left the Hospital one month previous to his present admission. At home, he was well for one week, when his asthma returned with its accustomed severity, necessitating 10 injections of adrenalin daily for the remaining three weeks. During the 48 hours preceding entrance to the Hospital, he suffered continuous asthma unrelieved by adrenalin.

On examination, he was seen to be a thin young man, acutely ill, breathing with great difficulty, inspiratory and expiratory; cyanotic and anxious. Lungs were filled with sibilant and sonorous râles; expiration was prolonged. Temperature was 101.4°; pulse 110; respiration 30. Roentgenogram of lungs was negative. For the next 12 days, he suffered almost continuously from varying grades of asthma, adrenalin infrequently affording temporary periods of relief.

The Douglas bag apparatus, with a mouthpiece and with a mask, as described above, was used. At first, pure oxygen was administered, without alleviation of dyspnea, although his color improved. A mixture of 80 per cent helium and 20 per cent oxygen was then admitted into the system. After he had inhaled six breaths, relief became manifest and in two minutes he was asleep, the retraction in his neck muscles having almost completely disappeared. Most of the sibilant and sonorous râles in his chest were no longer present. Oxygen was gradually substituted for helium and when the concentration of oxygen got as high as 30 per cent, dyspnea and râles returned. Administration of helium and oxygen again brought relief. That night, he was given 80 per cent helium and 20 per cent oxygen for one hour before

bedtime. He became relaxed, free from evident dyspnea, and slept restfully for six hours.

In this patient, attacks of asthma were almost always preceded by severe coughing spells. Attempts to abort these attacks with the inhalation of helium and oxygen were unsuccessful. At the conclusion of these violent seizures, dyspneic asthmatic breathing continued which was then relieved by inhalation of helium-oxygen mixtures. The extent of relief varied, depending upon the type of bronchiolar obstruction he was suffering from at the time. When the larger bronchioles appeared to be constricting, as suggested by sonorous râles in predominance, relief might be estimated to be between 90 and 100 per cent; if the fine bronchioles were constricting, as suggested by long-drawn-out piping and sibilant sounds, relief was estimated to be between 70 and 80 per cent.

The rest to his respiratory musculature was quickly apparent. His refractoriness to adrenalin gradually diminished, and the number of attacks lessened to two or three daily during the next two months. Helium, either through a mouthpiece or a mask, was given at intervals two to four times daily, for 15 minutes to 1 hour. Frequently, 85 per cent helium with 15 per cent oxygen was employed, since a greater degree of relief was obtained than with 80 per cent helium. The slight degree of anoxemia which the mixture induced seemed to be counter-balanced by the increased ease of penetration of the gas.

Therapeutic procedures aimed to cure the condition were not completely successful. Bacterial filtrates and vaccines were tried; residence in a dust-free room; oxygen chamber therapy; elimination diets; calcium and viosterol administration; postural drainage; radical maxillary sinus drainage; roentgen-ray therapy of sinuses and spleen; bronchoscopic treatments; psychotherapy. For a period of one month, helium and oxygen treatments were stopped. Asthma became gradually of the more continuous type; his adrenalin need increased to 5 and 6 injections daily. Helium and oxygen inhalations were instituted day and night for all continuous asthma—the mild attacks and the asthma that persisted after severe seizures. The number of asthmatic attacks decreased to 2 or 3 daily, relieved by adrenalin. Continuous asthma disappeared.

Inhalations of 15 to 20 per cent oxygen with 85 to 80 per cent helium were given after heating the inspired air to between 200 and 250° F. Only dry gas can be breathed at these high temperatures. Although the mouthpiece felt somewhat hot unless removed slightly from the teeth, the patient liked the sensation of the heated air in his chest and believed that he obtained more relief than from the mixture at room temperature. Furthermore, treatments were followed by expectoration of loosened watery mucus. However, it was not possible to abort a severe attack. When an acute asthmatic seizure commenced and gradually increased, the patient gave himself the helium-oxygen mixture for at times as long as 2 hours, with partial relief as long as he was inhaling it but with recurrence of severe asthma as soon as the mouthpiece was removed. The more continuous type of asthma responded much better to inhalation of helium-oxygen mixtures. Frequently, the patient asked for adrenalin because of pain in his ribs after he had had continuous asthma for a long period. This pain was completely relieved by breathing helium and oxygen without necessitating an injection of adrenalin. During the two months in which he was treated periodically, it became evident that refractoriness to adrenalin increased as he suffered more from continuous asthma, and that administration of helium-oxygen mixtures which relieved the continuous asthma was followed by disappearance of refractoriness to adrenalin. This effect may be ascribed probably not only to rest of the respiratory musculature but also to the other integral parts of the respiratory system, the bronchial and bronchiolar musculature, the decreased alveolar distention, the sympathetic nervous system, as well as the more conscious components of the psyche.

The following charts reveal some of the physiological effects of inhalation of helium and oxygen.

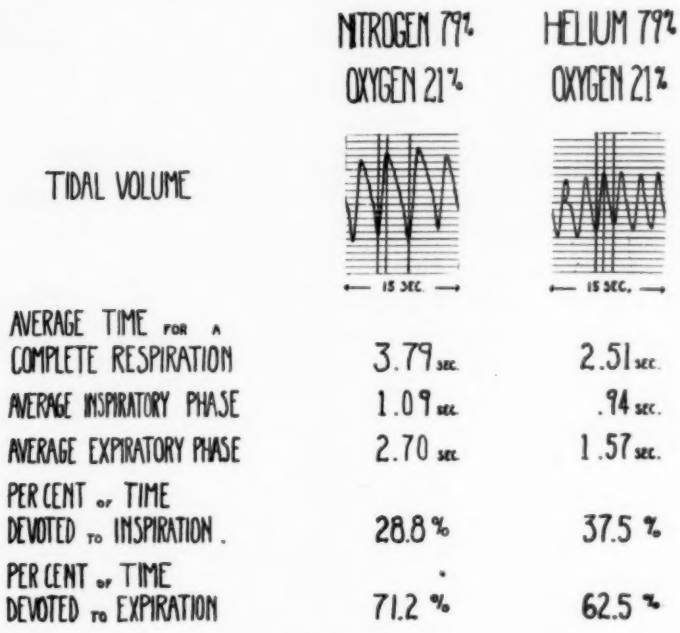


CHART 1

In the above chart (chart 1) a comparison of the respiratory cycle when the patient was breathing air and a helium-oxygen mixture was made during an attack of asthma. When air was breathed, the respiratory cycle was more prolonged and slow. The time occupied by expiration, both ab-

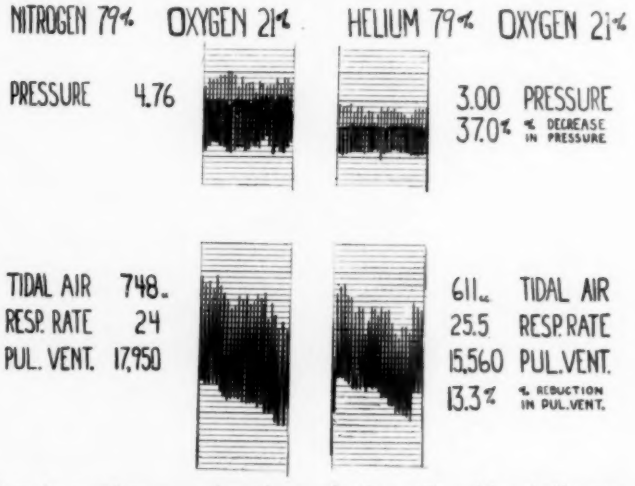


CHART 2. Patient in continuous asthmatic respiration. Breathing helium-oxygen mixture, pulmonary pressure reduced 37 per cent and pulmonary ventilation reduced 13.3 per cent.

solutely and relatively, was considerably less when the helium-oxygen mixture was inhaled. In addition, it can be observed that expiration, which is represented by the down-stroke of the graph, proceeds at a swifter pace at the very start of exhaling the helium-oxygen mixture, indicating a lessened time in which the alveoli are exposed to a distending expiratory pressure. In contrast, expiration takes place more slowly when air is breathed and with the maintenance of a higher pressure.

In the above chart (chart 2) comparison is made between the "pulmonary" pressure present when the patient breathed a helium-oxygen mixture and air. The decrease in this pressure is an index of the decreased effort involved. The actual pressure differences recorded in the graph represent in large part the work performed against the resistance in the testing apparatus itself, but it affords an insight into the relative differences in pressure required to move air and the lighter gas in obstructions that are placed in the interior of the respiratory tubal system, larynx, trachea, bronchi and bronchioles.

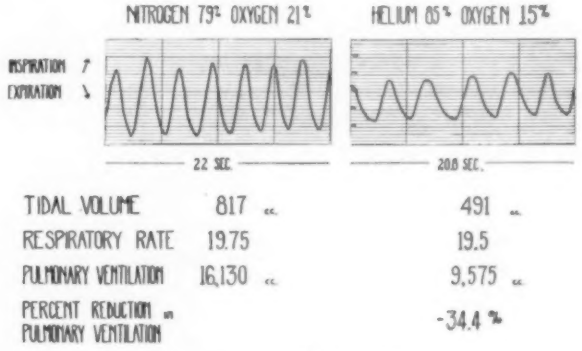


CHART 3. Patient in continuous asthmatic breathing. Increased rest period in each respiratory cycle and reduced pulmonary ventilation with helium-oxygen mixture.

In chart 3, the graph was obtained during a period of continuous asthma. The decrease in pulmonary ventilation is very apparent. There can also be observed a difference in the quality of the respiratory cycle. During inhalation of air, the sharp acute angles at each respiratory cycle indicate an absence of a rest period, which is shown to be present during inhalation of helium and oxygen by the more rounded shape of the curve, with a pause at the end of expiration. The ceaseless activity of the respiratory musculature during chronic continuous asthma plays a rôle in the production of the fatigue which this type of patient suffers from and is probably involved along with other factors touched upon above in the development of refractoriness to adrenalin. In some attacks of acute severe asthma, although helium-oxygen inhalations decrease the need for increased pulmonary ventilations, the rest period is not produced, as is shown in the following

chart (chart 4). It is probably that this variation in response is dependent upon the size of the bronchioles that are most affected; the smaller the orifice the more difficult it becomes to give maximal relief.

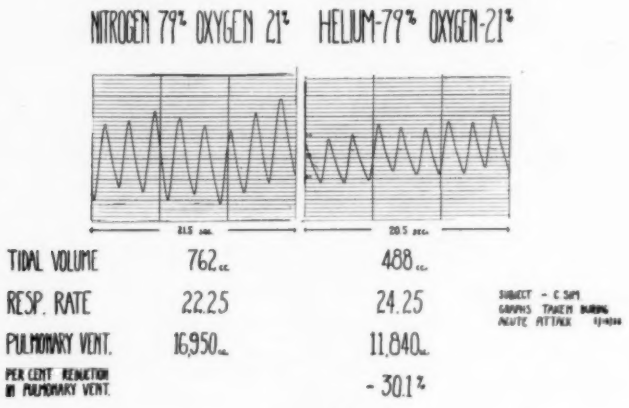


CHART 4

In this patient, the pulmonary ventilation during asthmatic seizures was increased almost three to four times his resting ventilation. This fact itself is of considerable interest and will be commented upon later. The effect of inhalation of helium-oxygen mixtures is almost always to decrease both the pulmonary ventilation and the tidal air.

Case 2. Male, age 22 years. Past History: At the age of three, the patient had tuberculous glands removed from his neck. Following this, he developed bone tuberculosis and was in a tuberculosis sanatorium at six and again at fifteen. He had repeated attacks of head colds and bronchitis up to four years ago. Present Illness: Two and a half months ago, the patient first developed asthmatic breathing, and two weeks later he suffered a severe asthmatic attack which lasted three days. Since then, he has had asthma intermittently. On admission, he was seen to be a fairly well-developed man of 22, in typical asthmatic breathing. Lungs were filled with sibilant and sonorous râles, without dullness; expiration prolonged. He continued to wheeze for one week, when he contracted bronchitis with fever. His asthma then cleared for two weeks. During the seventh week, he caught a head cold, which was improving when he suddenly began to wheeze. The asthmatic attack became progressively worse, unrelieved by adrenalin in repeated doses, or by morphine or atropine. He became cyanotic and was placed in an oxygen tent with 60 per cent oxygen. His color improved but asthmatic breathing persisted. His pulse gradually became weaker and at the end of 20 hours almost imperceptible. He was comatose. The breathing was in shallow gasps; the rate had declined to 15 times a minute. He appeared to be in imminent danger of respiratory failure. Alphalobelin, 3/20 of a grain, was given intramuscularly, with temporary increase in rate of respiration and marked accentuation of retraction signs in the neck muscles. Within five minutes, breathing again became slow, shallow and gasping.

A mixture of approximately 75 per cent helium and 20 per cent oxygen was obtained in the tent (the remainder water vapor and nitrogen), and within half an hour the patient became conscious, retraction signs in the neck muscles diminished, improvement became progressive. In two and a half hours, the patient was com-

pletely comfortable in the tent; there was no neck muscle retraction; breathing had increased to 20 per minute; the pulse was of fairly good quality and the tent was removed. In about 15 seconds, the visible signs of asthma returned, accompanied by neck muscle retraction. However, the patient was rested, cheerful and out of danger. His subsequent attacks responded promptly to adrenalin. One week later, he returned home suffering from occasional attacks, and attempted to find work. Four months later, he was in good health, not inconvenienced appreciably by occasional attacks, which promptly responded to adrenalin.

In this patient, the inhalation of a helium-oxygen mixture was followed by what appeared to be an *increase* in pulmonary ventilation. He was too ill to permit getting a record of his tidal air, but the clinical impression was unmistakable that he had an increased depth and an increased rate of respiration while he was inhaling the helium-oxygen gas. The respiratory musculature, which seemed on the verge of complete cessation of activity, was rested to such an extent after two and a half hours that the patient was able to tolerate without discomfort the moderate degree of asthma which returned when the tent was removed.

Case 3. Female, age 40 years. Family History: One sister and a grandmother had asthma.

Present Illness: Asthmatic attacks began two years ago. Since then, she has had four hospital admissions for severe asthma. Tonsillectomy, administration of bacterial filtrates and vaccines, drainage of sinuses and establishment of permanent antral openings, postural drainage and psychiatric interviews, were followed by no improvement. In the hospital, the asthmatic attacks always abated on residence in an oxygen tent for 10 days to three weeks, and twice in the filtered air room. After being home from the hospital for one week, she again returned with severe asthma. On examination, she was a thin, poorly nourished woman in severe asthmatic breathing. Lungs showed dullness and fine crepitant râles at right base and widespread sibilant and sonorous râles. Expiration was markedly prolonged. She was gradually improved by adrenalin, 6 to 8 c.c. daily, oxygen tent with 50 to 60 per cent oxygen, codeine, bromides and iodides. However, on the sixth week of residence in the hospital, the attacks became steadily more frequent, ending in continuous asthma for 48 hours. Adrenalin, large doses of nembutal and oxygen in the tent did not relieve her. She was aroused with difficulty and then was irrational, no doubt partly due to nembutal and bromides. Sibilant and sonorous râles persisted throughout her lungs. She was taken out of the tent and a mask attached to her face. At first, she struggled against the mask but after 15 minutes of inhaling 18 to 20 per cent oxygen and 82 to 80 per cent helium, she was relaxed and accepted the treatment willingly. The relief of her dyspnea was noticeable and one hour later treatment was discontinued. Approximately 90 per cent of the râles had disappeared and did not return that afternoon. She was both subjectively and objectively relieved of asthma. An attack the following day was promptly relieved by adrenalin. She gradually improved, helium and oxygen being administered at intervals for three days. For two weeks she required no adrenalin, when wheezing and coughing returned, necessitating for two additional weeks two to four injections of adrenalin daily. Attacks cleared up during the subsequent week and the patient left the hospital temporarily free from asthma.

The use of helium-oxygen mixtures in this patient was followed by a clearing up of a persistent siege of continuous exhausting asthma and by

disappearance of refractoriness to adrenalin. The patient was a difficult one to handle since she attributed her asthmatic attacks to the most recent antecedent treatment. The various procedures which were attempted had all to be abandoned without a satisfactory trial for this reason.

Case 4. Male, age 52 years. Past History: Patient had had a chronic post-nasal discharge for six years following a head cold. Present Illness: Asthmatic attacks began five years ago. His first admission to this hospital was two years ago when he complained of almost steady asthma for the preceding three weeks. Allergic study was negative. External ethmoidectomy and later frontal sinusectomy were performed. Following the latter procedure, asthmatic attacks were said to have become worse. Five days before admission, he went into status asthmaticus and entered the hospital almost moribund. On physical examination, he was a middle-aged man, thin and worn looking, obviously in extremis. His hands and feet were cold; respirations were very shallow and slightly labored; lungs contained a few scattered squeaks and whines. There was slight dullness in the right anterior chest with suppressed breath sounds. Heart was not enlarged; sounds were of very poor quality. Pulse was poor; rate 110; vessel wall sclerotic. W. b. c. 22,700; polynuclear percentage 79. Patient seemed about to expire when he reached the ward. He was put into an oxygen tent in an oxygen concentration of 50 to 60 per cent. He was given morphine and atropine, and caffeine sodium benzoate 0.6 gram. The latter medications appeared to be followed by striking improvement in general condition, but status asthmaticus continued. On the following day, inhalations of helium 80 per cent and oxygen 20 per cent were begun for periods of one hour. After the first inhalation, the patient became temporarily better, relaxed and relieved of asthma. Return of symptoms of the same severity was treated with adrenalin with little relief. A second period of inhalation of helium and oxygen for one hour was again followed by relaxation, sleep and freedom from asthma. Return of symptoms several hours later was again treated by adrenalin which this time was followed by disappearance of asthma. Patient was treated intermittently with helium-oxygen inhalations for the next two days, but following the disappearance of his refractoriness to adrenalin the patient preferred the injection to breathing through a mask. He progressively improved, leaving the ward three and a half weeks later, requiring at that time 1 to 2 injections of adrenalin in 24 hours.

In this patient, the administration of helium-oxygen mixtures for periods of one hour at a time was followed by interruption of a profoundly severe asthmatic state, temporary relief of asthma and disappearance of refractoriness to adrenalin.

B. Obstructive Lesions in the Trachea and Larynx. Two patients with carcinoma of the larynx had previously been subjected to tracheotomy. When the tube was closed, a test was made of the effect of inhalation of a helium-oxygen mixture as contrasted to air. Relief was experienced in both cases, in one almost complete. A third patient with esophageal carcinoma was given helium-oxygen inhalations with marked relief of dyspnea and stridor, until an acute exacerbation of symptoms took place, necessitating tracheotomy. Measurement of the "pulmonary" pressure in one case of laryngeal carcinoma showed the same type of decreased pressure when the helium-oxygen mixture was breathed instead of air, as was shown in the first asthma patient reported in the previous section. The first case to be reported in detail is that of laryngeal edema in an infant.

Case 5. Boy, age 4 months. Patient had had a head cold with a cough for six weeks when suddenly his breathing became difficult and wheezy. His subsequent history revealed that he swallowed "something green" at 9 a.m. On examination late that afternoon, he was seen to be a fairly well developed boy of four months. His respirations were accompanied by a sound which seemed to be produced near the larynx. Lungs were negative except for occasional wheezing sounds. Roentgen-ray showed a speck in the infra-glottic region. Laryngoscopy was done, followed by esophagoscopy, with removal of a green tack from the esophagus. On the following evening, he became markedly dyspneic, with retraction of neck muscles, cyanosis and restlessness. Administration of 90 per cent oxygen in a tent cleared the cyanosis but gave no relief to his dyspnea. Helium was then added to a concentration of 80 per cent; oxygen concentration 20 per cent. The boy became obviously more comfortable within a few minutes, with relief of dyspnea but with perceptible cyanosis. Oxygen was then increased to 30 per cent, helium 70 per cent. Color was then pink and dyspnea absent. He was given codeine. At 6 a.m. the following morning, he was fed and changed outside the tent. Marked difficulty in breathing and restlessness returned. After about six to eight coughing spells, between each one of which he had a free interval, a tracheotomy was done at 3 p.m. Patient was then comfortable for a time when severe dyspnea again developed. During the following five days, he had to be repeatedly bronchoscoped or aspirated to remove mucus plugging the bronchi. He developed bronchopneumonia during this period and died six days after tracheotomy. At autopsy, a diffuse bronchopneumonia was found but no laryngeal obstruction or edema.

In this case, the continuous inhalation of 70 per cent helium and 30 per cent oxygen relieved the obstructive dyspnea and cleared the cyanosis, whereas 90 per cent oxygen removed the cyanotic color but did not give any relief to the urgent obstructive dyspnea. In this kind of lesion, residence in a helium-oxygen tent until the acute process in the larynx subsides would appear to be a rational procedure. Laryngeal obstruction may occur as a result of trauma, or in the course of infectious diseases such as diphtheria, or as a consequence of tumors. In any instance where a resolution of the obstruction may be expected, inhalation of helium-oxygen mixtures might tide the patient over the period of obstruction.

Case 6. Female, age 6 weeks. The patient suffered from stridor since birth. Three days before admission, her condition became worse and she choked on eating. During her examination in the out-patient department she had an acute respiratory collapse and was admitted as an emergency. On examination, she was a well-developed infant, gasping at each breath. On inspiration, there was marked retraction of suprasternal, intercostal, sub-xiphoid and subcostal spaces. She became markedly cyanotic on crying. Lungs were clear. The administration of 90 to 100 per cent oxygen in the helium-oxygen tent removed most of the cyanosis but did not relieve the dyspnea. When 68 per cent helium and 24 per cent oxygen were given, the dyspnea was very much relieved. The retraction of the neck muscles disappeared but slight sub-xiphoid retraction was evident. The helium employed at that time was put into the tanks as an emergency measure and was only 94 per cent pure.* Undoubtedly, even better results would have been secured if pure helium had then been available. As it was, her respirations declined to 20 per minute in the tent atmosphere of helium and oxygen; she slept peacefully and could take her nourishment

* Two to 3 per cent of the atmosphere was water vapor. The density of water vapor is less than that of air but much more than a helium-oxygen mixture. Calcium chloride was used in addition to ice to dry the air in some instances.

without effort. When she was taken out of the tent, the respiratory rate accelerated to 40 per minute; marked retraction of all the accessory muscles of respiration became manifest; she became restless and unable to take her feedings. She was kept in the helium-oxygen atmosphere for eight days in the hope that the obstructive process might clear. No improvement in her condition when outside the tent took place and a tracheotomy was performed. The obstruction was found to be just above the bifurcation, its nature not discovered. Following the tracheotomy, she developed a bilateral pneumothorax with urgent dyspnea. This was relieved only when the oxygen concentration was kept above 90 per cent. At the end of 16 hours, it was reduced to 50 per cent, and in 3 days discontinued. The baby was well one month after tracheotomy, except that repeated aspirations of the trachea were necessary. Three months later, she died suddenly. At autopsy, the tracheotomy tube was found to have eroded a soft tumor in the tracheal wall and ruptured the innominate artery.

In this infant, the relief of dyspnea afforded by inhalation of a helium-oxygen mixture was striking. Had the lesion been of the type that might have resolved, she could have been kept in the tent atmosphere for an indefinite period. The dyspnea that took place when the lungs were suddenly collapsed was not obstructive but rather dyspnea dependent upon acute oxygen-want. It was exceedingly interesting to observe the different pathogenesis of dyspnea in this child. In considering the dyspnea due to the pneumothorax, it was instructive that the inhalation of 50 per cent oxygen was without any discernible effect on the dyspnea; in fact, it was not until concentrations above 90 per cent were administered that the dyspnea was relieved. These high concentrations of oxygen are dangerous for periods exceeding 12 to 16 hours daily and should generally be relinquished for concentrations below 60 per cent for the remainder of the 24 hours. Over long periods of time, such as two or more weeks, concentrations of over 90 per cent oxygen should not be given, even when limited to 12 hours daily.*

In these two patients, a slight increase in the oxygen concentration of the helium mixture above 21 per cent (between 24 and 30 per cent) appeared clinically more beneficial than lower oxygen concentrations. Not only was the cyanosis relieved with the added oxygen but the patients themselves seemed less restless. An opposite response was obtained in the patients with severe chronic continuous asthma, in whom 17 per cent oxygen and 83 per cent helium were generally clinically superior to higher oxygen concentrations. It was observed that 21 per cent oxygen in helium when administered to the infants with laryngeal and tracheal obstruction did not overcome the marked cyanotic color, and lower oxygen concentrations definitely increased the cyanosis and restlessness. However, in the patients with asthma, during continuous asthmatic respiration, there was only slight

* In work to be published on the effect of high oxygen concentrations on white mice, it was shown that animals survived 12 hours a day pure oxygen, with 50 per cent oxygen the remainder of the time, but that pathologic section of the lungs revealed in many cases organizing pneumonia. The use of concentrations of oxygen as high as 90 per cent should not be discarded for emergency conditions, when it may be of critical importance to administer them, but their employment over long periods does not seem warranted in view of experimental evidence.

cyanosis during the breathing of 21 per cent oxygen in helium, and there was but very slight and sometimes imperceptible increase in cyanosis when the oxygen concentration was still further reduced, such as to 17 or 18 per cent, with obvious increase in comfort. Obviously, the lower oxygen concentration was attempted in order to give as much helium and therefore as much physical relief as possible.

These differences in clinical response to the oxygen concentration in the helium mixture have been somewhat clarified by dog experiments which are to be reported separately. It appears likely that higher intrapleural negative pressures take place in laryngeal and tracheal obstruction than in asthma, and that with these markedly elevated negative pressures, there occurs a congestion and edema of the lungs, the lung being subjected to a kind of "dry cupping," which produces a more serious anoxemia and circulatory failure in laryngo-tracheal obstruction than is generally present in chronic continuous asthma, accounting for the greater benefit obtained by increased oxygen tension in these conditions. In general, the precise dosage of helium and oxygen will have to be estimated by gauging the degree to which anoxemia or respiratory fatigue is involved.

Discussion of Results

Although four cases of asthma are insufficient for a final evaluation of the rôle of helium in the treatment of this disease, the beneficial effects which were obtained had sufficient uniformity to permit certain observations concerning the physiologic effects of this gas administered with oxygen.

When the patient was experiencing more or less continuous asthma, relief was obtained by the inhalation of 80 to 85 per cent helium with 20 to 15 per cent oxygen. The character of the spasm appeared to determine whether the dyspnea was alleviated completely or partially. When the râles were predominantly of the thin, long-drawn-out, piping quality, the removal of the sensation of air-hunger was less marked than when more sonorous râles were present, suggesting involvement of the larger size bronchioles. Relief was felt after six to 10 breaths, as the nitrogen in the pulmonary residual air was replaced by helium. Objectively, the signs of over-activity of the accessory muscles of respiration, such as those in the neck, were diminished, or, in some cases, disappeared. If the treatment was given for a short period, such as five minutes, return to respiration of air was followed in three to four breaths by recurrence of asthmatic breathing. When the inhalation of the helium-oxygen mixture was continued for an hour or more, the patient frequently, although not always, had a period of relief from asthma for six to eight hours. Furthermore, repeated inhalations for the more moderate, continuous asthma were apt to be followed by the disappearance of refractoriness to adrenalin and the clearing of asthma between attacks.

In three cases in which refractoriness to adrenalin became so marked

as to result in a serious or even grave condition, the inhalation of helium-oxygen gas produced a striking alteration of the clinical picture. The patients were either stuporous or comatose; the dyspnea suggested a decreased ventilation because it was slow and gasping; the pulse was rapid and poor in quality; cyanosis was marked without oxygen; retraction signs in the neck muscles were less marked than in an acute attack; the lung signs showed thin, piping sounds with long-drawn-out respirations distinctly less noisy than in an acute attack. The end-state of status asthmaticus suggested a type of respiratory failure in which the muscles of respiration were exhausted to the point of impending cessation of activity. Although in these cases the severity of their condition precluded measurements of the tidal air, the pulmonary ventilation seemed diminished and anoxemia was present. The inhalation of helium-oxygen gas for one to two and a half hours was followed by complete disappearance of asthma, both subjectively and objectively, with return of consciousness and improvement of the pulse. In one case, recurrence of moderate asthma took place immediately; in the others, two and six hours after cessation of treatment. In these cases, the inhalation of helium-oxygen gas provided rest to the respiratory apparatus; an increased tidal air (clinically observed), and a state in which adrenalin was effective again in stopping bronchial spasm. The patients became ambulatory and were discharged from the ward.

Acute attacks of asthma were not aborted by helium-oxygen mixtures, nor, although their severity was diminished during the inhalation of the gas, were they sufficiently relieved to displace adrenalin when this drug was effective. The persistence of asthma of variable extent, in those instances when the patient did not receive complete or lasting relief from adrenalin, was the indication for the employment of helium-oxygen mixtures.

In the first patient, more or less continuous asthma dominated the clinical picture without, however, going over into a severe status asthmaticus. Graphic records during continuous asthma showed a marked increase in pulmonary ventilation, which was decreased when helium-oxygen gas was breathed. Furthermore, the ventilation was reduced, even when only 15 per cent oxygen was inspired in the helium mixture. An interpretation of this clinically observed fact, that the inhalation of the lighter helium-oxygen mixture diminished the need for an increased pulmonary ventilation, leads to the suggestion that the primary cause for the sensation of air-hunger in this type of asthma is neither the presence of anoxemia nor CO_2 excess but rather an interference with the habitual rate of filling and emptying the lungs. The increased effort required to obtain the normal velocity of air delivered to and from the lungs appears to give the sensation of dyspnea and represents an *equilibrium* that functions to a degree independently of the respiratory gaseous exchange. Davies, Haldane and Priestley [11] first carefully studied the respiratory response to resistance, and recognized that interference with the normal stimulation of the Hering-Breuer reflex initiated the feeling of air-hunger.

Obviously, the maintenance of a sufficient oxygen saturation of the blood and an adequate removal of CO_2 are basic impulses that determine respiration in health and disease, but in the patient with asthma in whom three to four times his normal ventilation is provided during the period of bronchial spasm, these basic factors are not the initial cause of the sensation of dyspnea. In the first place, inhalation of pure oxygen removed the cyanosis without affecting the dyspnea. Secondly, inhalation of 15 per cent oxygen, which slightly increased the cyanosis, afforded relief when it was mixed with helium instead of nitrogen. That anoxemia is not the main cause of this type of dyspnea was evident also in the case of laryngeal obstruction that had an increased pulmonary ventilation. The feeling of air-hunger was relieved when the concentration of oxygen was 24 per cent, provided it was administered with helium instead of nitrogen. That CO_2 excess is not the cause of the increased ventilation may be reasonably inferred from the fact that CO_2 is 25 times as diffusible as oxygen (in water) and that the pulmonary epithelium shows no inability to eliminate CO_2 in high concentrations if the needs of the body for oxygen are met. Richards and the author [12] have shown that CO_2 may be eliminated from passively congested, fibrotic or tuberculous lungs at a tension two or more times the usual concentration if the patient is provided with an adequate oxygen supply.* Meakins [13] has reported tensions of CO_2 in the arterial blood of asthma patients which may be normal, lowered or elevated, depending on the type of asthmatic seizure. During periods of increased ventilation, the CO_2 is diminished.

The onset of air-hunger in patients with asthma and obstructive lesions in the larynx is, therefore, in part a reaction to an interference with the normal rate of filling and emptying the lungs. The sensation of the volume of air delivered to the lungs per breath is presumably interpreted through the Hering-Breuer reflex arc, which is operative in stimulating and terminating normal inspiration. The existence of an equilibrium designed to maintain an entrance into the lungs of an accustomed volume of air at an accustomed velocity is of considerable importance to recognize, for it appears to be responsible to a large extent for the strenuous efforts which the patient with asthma exerts in the attempt to maintain it. That a purely physical sensation of an adequate inlet of air into the lungs, separate from other chemical equilibria, is an essential factor in obstructive dyspnea is additionally confirmed by the exhaustion which the asthma patient develops by carrying on a pulmonary ventilation three to four times the normal for him, and by his response to the inhalation of a lighter gas of the same oxygen concentration. In the first case reported, the patient breathed an 80 per cent helium-20 per cent oxygen mixture during a period of continuous asthma and within two minutes showed a fall in pulmonary ventilation, relief of dyspnea and onset

* Calculations of Loewy and Zuntz have indicated that 1 mm. O_2 pressure difference suffices for the diffusion of 250 c.c. of O_2 per minute and 40 times this quantity of CO_2. (Quoted from Wiggers, C.: The physiology of health and disease, 1934, Lea and Febiger, Philadelphia.)

of sleep. When 100 per cent oxygen was then substituted for the helium-oxygen mixture, dyspnea and increased ventilation recurred.

That mixtures of oxygen and helium, when inhaled through the bronchial tree, may result in a swifter diffusion of oxygen through the pulmonary epithelium, and that the relief experienced by the patient may be due to the satisfaction of his oxygen-want must be considered. Undoubtedly, the lightness of the gas makes it possible for the oxygen molecule in the presence of a high concentration of helium to travel at a high velocity, with less pressure in the pulmonary air-way; therefore, more oxygen (as well as helium) molecules at the start of inspiration will travel through the small bronchioles into the alveoli than when air is breathed. The lessened pulmonary ventilation and air-hunger may conceivably be in part dependent on better oxygenation. That this is not the predominant causal factor in the relief experienced is shown by the fact that under certain circumstances 85 per cent helium and 15 per cent oxygen will result in an alleviation of dyspnea, even though there can be observed a slight increase in cyanosis. A prolonged administration of 15 per cent oxygen with helium would be regarded unfavorably as the known consequences of anoxemia would ultimately aggravate the condition, but at the onset of treatment it has appeared useful at times to start with this mixture, because a greater relief was felt by the patient. Later the oxygen is increased to a 20 per cent concentration.

Additional evidence for the existence of this kind of equilibrium is easily obtained by having a normal individual breathe through an orifice ⅛ of an inch in diameter. The sensation of air-hunger is quickly produced even with an intact respiratory apparatus, without the production of anoxemia or CO_2 accumulation; the inhalation of 15 per cent oxygen and 85 per cent helium, despite the production of a slight anoxemia, results in an immediate diminution of the sensation of air-hunger. This response can safely be ascribed to the swifter and easier movement in and out of the lungs of the lighter gas.

In the infant with obstruction in the trachea, the respiratory rate in air was 40 per minute and the clinical signs of respiratory obstruction were evident. When the helium-oxygen mixture was inhaled in the tent, the rate fell to 20 per minute, with marked relief of dyspnea.* That the presence or absence of anoxemia is also involved as a basic factor was revealed by the behavior of this infant as well as by that of the infant with laryngeal edema. In both instances, a greater degree of comfort was produced when the oxygen was raised slightly above 21 per cent, in one case to 24 or 25 per cent oxygen and in the other to 28 to 30 per cent oxygen. However, when the oxygen concentration was further increased, dyspnea of the obstructive type recurred. An instructive occurrence was the behavior of the child with tracheal obstruction after the development of pneumothorax. The degree of anoxemia produced by involvement of both lungs was so severe

* This sequence was vividly revealed by motion pictures taken with the infant in and out of the tent.

as to require for 16 hours the inhalation of 90 to 100 per cent oxygen to obtain relief from dyspnea. That these high concentrations when continued over long periods are accompanied by the danger of pulmonary irritation has been commented upon but it is of importance to recognize their possible value in such emergencies as arose in this case. Withdrawal of air from the pleural cavity was of great and immediate benefit. An additional manifestation of the relief of dyspnea by the purely physical function of helium, independent of any chemical factor such as anoxemia or CO_2 excess, was shown by the following record of a man with paroxysmal cardiac dyspnea. For our present purpose, it is unnecessary to review in detail his clinical history. He was a man of 60 years, with pulmonary emphysema, chronic nephritis and myocardial fibrosis. His chief complaint was sudden, severe dyspnea which came on in attacks generally at night. Inspection of

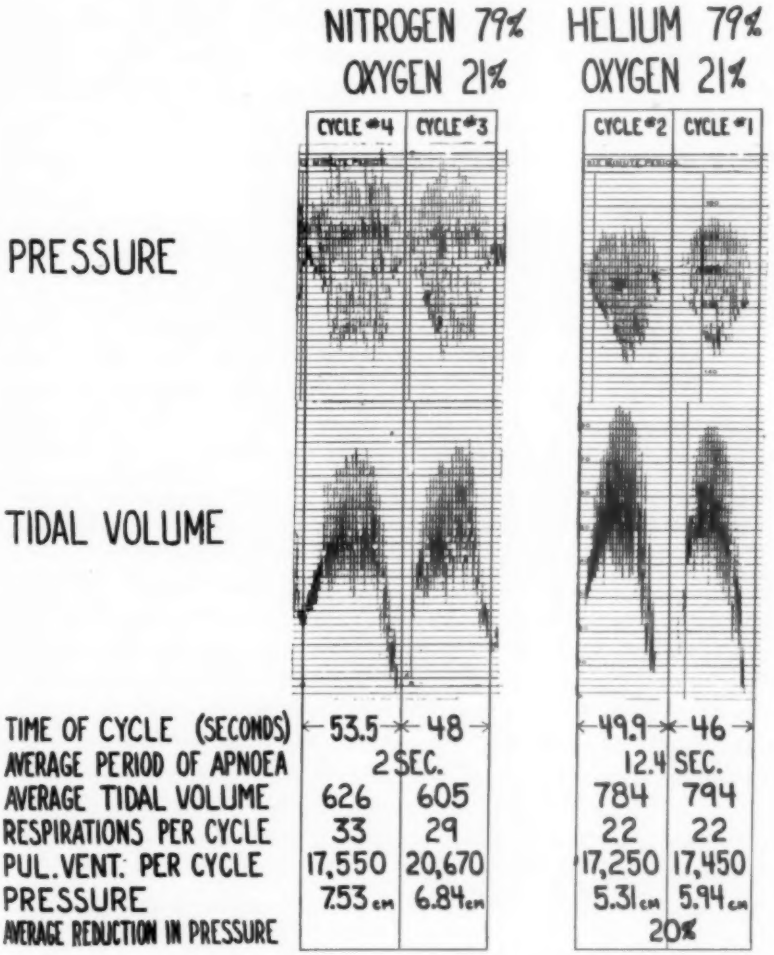


CHART 5. Patient in severe Cheyne-Stokes dyspnea. Increased tidal volume during inhalation of helium-oxygen mixture with decrease in sensation of air-hunger.

these attacks revealed periodic respiration with a dyspneic phase of unusual severity. In the accompanying chart (chart 5), the graph of his pulmonary ventilation shows the very markedly increased tidal air (800 c.c.) which he breathed at the height of dyspnea. The patient could barely retain the mouthpiece because of the urgent sensation of air-hunger. When 100 per cent oxygen was inhaled, his breathing became regular, with immediate relief of dyspnea, which illustrates the chemical factor in the causation of this type of cardiac dyspnea.

When the patient inhaled a mixture of 80 per cent helium and 20 per cent oxygen, the dyspneic periods were characterized by an even greater tidal air (up to 940 c.c.) than when he was breathing air and the apneic periods were increased (chart 5). His sensation of air-hunger was diminished, notwithstanding the relatively great respiratory excursion, due to the ease with which these large volumes of light gas entered and left the lungs.* During quiet breathing, no difference can be detected between the inhalation of air and helium-oxygen mixtures. When excessive volumes of air are brought into the chest, muscular effort is appreciable and under these circumstances the lighter gas mixtures require less effort on the part of the respiratory musculature, with a resulting decrease in the sensation of air-hunger. The consciousness of dyspnea is thus in part dependent on the nerve pathways which connect the muscles utilized in ventilating the lungs with the brain. Dyspnea is relieved, when the effort made by these muscles can be decreased, either (1) by supplying a lighter respirable gas which physically decreases the amount of work done, or (2) by chemically reducing the amount of ventilatory work necessary, such as by decreasing the total oxygen consumption or by providing an increased oxygen concentration in the inhaled air.

The interpretation of the dyspneic state requires an understanding of all the influences that bring it about. Harrison,[14] in discussing the dyspnea provoked by mild exertion in cardiac states, says that it is not related to the blood gases, the blood flow or the pH of the blood but is caused by disturbances in the proprioceptive reflexes arising in the lung. He emphasizes the factor of lung stiffening and lowered vital capacity. There appears to be little doubt that the sensation of dyspnea is experienced within the brain as a consequence of impulses sent along nerve pathways from the lungs and respiratory musculature; however, the evolution of the dyspneic state in a patient with congestive heart failure or with paroxysmal dyspnea is profoundly concerned with the blood gases, oxygen and carbon dioxide, the blood flow and the pH of the blood. The increased pulmonary ventilation, which is a constant phenomenon in the dyspnea of heart disease, may be diminished in a number of ways, for example, by lowering the total oxygen consumption by thyroid ablation [15] or by inhaling oxygen-enriched atmospheres. The moment pul-

* The longer periods of apnea present when helium-oxygen gas was breathed was probably due to the excessive washing out of CO_2 which the large tidal air volumes accomplished, as well as maximal saturation of the hemoglobin in the arterial blood.

monary ventilation is reduced, the sensation of dyspnea is reduced. Since the basic purpose of ventilating the lungs is to provide oxygen to the arterial blood and the tissues, eliminating carbon dioxide at the same time, the basic cause of the dyspneic state must be sought for in a disturbance in this equilibrium, which does involve the blood gases, the blood flow and the pH of the tissues.* Richards and the author [12] have repeatedly observed the dyspnea of heart failure relieved by the inhalation of 50 per cent oxygen, accompanied by a decrease in pulmonary ventilation, a slower pulse rate, an increased arterial oxygen saturation and an elevated arterial CO_2 content. The lowered oxygen tension in the blood or tissues admittedly does not itself arouse the sensation of air-hunger, but it is responsible, together with the necessity of maintaining a suitable pH equilibrium, for much of the increase in pulmonary ventilation which characterizes the dyspnea of cardiac failure. It is this increase in pulmonary ventilation in the presence of disabled lungs that stimulates the proprioceptive reflexes referred to. It has appeared necessary to us to limit the significance of the nervous reflex cause of dyspnea in heart disease in order to make clear its special importance in the experience of air-hunger in asthma and obstructive conditions in the respiratory tubal system.

Summary

The specific gravity of helium being one-seventh that of nitrogen, a mixture of 80 per cent helium and 20 per cent oxygen has one-third the weight of a comparable volume of air. Since the pressure required to move an object is in general proportional to its weight, it was assumed that a relatively light respirable gas could be breathed with less effort in clinical conditions in which difficulty in ventilating the lungs was present.

In four patients with severe asthma, inhalation of helium-oxygen mixtures appeared to be of considerable benefit. When continuous asthma was present, subjective and objective relief were obtained. In three patients, a serious or grave state of status asthmaticus and refractoriness to adrenalin were removed by inhalation of helium-oxygen mixtures. The acute attack of asthma was not aborted, and the relief obtained by inhalation of various mixtures of helium and oxygen was not sufficient to replace adrenalin when this drug was effective. The special value of helium-oxygen mixtures is in the treatment of asthma persisting after adrenalin and in status asthmaticus.

Graphic records of the quantitative and qualitative changes in pulmonary ventilation revealed the following consequences of inhalation of

*The argument that the patient with congenital heart disease may have a low arterial saturation without dyspnea does not take into account the admitted acclimatization mechanism whereby individuals superficially adapt themselves to oxygen-want. The comparison may be made with the effect of morphine in addicts, in which large doses may not provoke sleep; similarly, large doses in unacclimatized individuals not only produce sleep but may indeed be fatal. In both instances, the compensatory adjustments that develop are inadequate to protect the individual. The point involved is that acute oxygen-want acts as a chemical stimulus to breathing, perhaps largely through the carotid sinus reflex, and as such is frequently a factor in increasing the pulmonary ventilation of the dyspneic patient.

helium-oxygen mixtures on a patient with continuous asthma: (1) decrease in pulmonary ventilation; (2) decrease in pulmonary pressure; (3) relative and absolute diminution in the length of expiration; and (4) increased rest period between respiratory cycles. The decreased pulmonary pressure and the swifter flow of gas during the early phase of expiration would appear to lessen the likelihood of alveolar distention and emphysema in patients who have much continuous asthma.

Severe obstructive dyspnea in two infants, one with laryngeal and the other with tracheal obstruction, was relieved by inhalation of helium-oxygen mixtures. In one of these cases, the infant was comfortable in a helium-oxygen tent for eight days, but the congenital nature of the obstruction was such as to require tracheotomy ultimately. In conditions of laryngeal or tracheal obstruction in which there is a possibility of the obstruction clearing up, the inhalation of helium-oxygen atmospheres may be useful by providing relief from a severe form of air-hunger and its consequent fatigue of the respiratory musculature.

The relief of dyspnea in patients suffering from various type of respiratory obstruction during the inhalation of helium-oxygen mixtures made evident the importance of an accustomed volume flow of gas to and from the lungs. This special equilibrium, i.e., the maintenance of a certain required pulmonary air flow, is regulated by proprioceptive reflexes from the lungs and the respiratory musculature. Disturbance in this equilibrium is the primary cause of the sensation of air hunger in this type of dyspnea; anoxemia may occur in severe cases as a secondary complicating factor.

BIBLIOGRAPHY

1. Barach, A. L.: Use of helium as new therapeutic gas, Proc. Soc. Exper. Biol. and Med., 1934, xxxii, 462–464.
2. Barach, A. L.: Treatment of heart failure by continuous oxygen therapy, Anesth. and Analg., 1935, xiv, 79–88.
3. Jannsen and Lockyer: Quoted from National Encyclopedia, 1932, v, 222, P. F. Collier and Son.
4. Ramsay, Sir W.: The gases of the atmosphere, 3rd Ed., 1905, Macmillan and Co., London.
5. Cooke, C.: U. S. Patent Office, 1923, Patent No. 1,473,337.
6. Sayers, R. R., and Yant, W. P.: Value of helium-oxygen atmosphere in diving and caisson operations, Anesth. and Analg., 1926, v, 127–138.
7. Hershey, J. W.: Physiological effects of oxygen atmospheres diluted by nitrogen, Trans. Kans. Acad. Sci., 1929, xxxii, 51.
8. Barach, A. L.: Rare gases not essential to life, Science, 1934, lxxx, 593.
9. Forrer, A.: Research on respiration of dry overheated air, Arch. d. sc. biol., 1934, xx, 30.
10. Barach, A. L.: New oxygen tent, Jr. Am. Med. Assoc., 1926, lxxxvii, 1213–1214. Importance of ventilation in oxygen tent and oxygen chamber therapy, N. Y. State Jr. Med., 1931, xxxi, 1263–1266.
11. Davies, H. W., Haldane, J. S., and Priestley, J. G.: Response to respiratory resistance, Jr. Physiol., 1919, liii, 60.
12. Barach, A. L., Richards, D. W., Milhorat, A. T., and Levy, R. L.: Effects of oxygen therapy on patients with congestive heart failure, Proc. Soc. Exper. Biol. and Med., 1929–30, xxvii, 308.

BARACH, A. L., and RICHARDS, D. W., JR.: Effects of treatment with oxygen in cardiac failure, Arch. Int. Med., 1931, xlviii, 325–347.

RICHARDS, D. W., JR., and BARACH, A. L.: Effects of oxygen treatment over long periods of time in patients with pulmonary fibrosis, Am. Rev. Tuberc., 1932, xxvi, 253–260.

RICHARDS, D. W., and BARACH, A. L.: Oxygen therapy in pulmonary tuberculosis, Am. Rev. Tuberc., 1932, xxvi, 241.

RICHARDS, D. W., JR., and BARACH, A. L.: Prolonged residence in high oxygen atmospheres, Quart. Jr. Med., 1934, iii, 437–466.

13. MEAKINS, J. C., and DAVIES, H. W.: Respiratory function in disease, 1925, Oliver and Boyd, Edinburgh, page 196.

14. HARRISON, T. R.: Failure of the circulation, 1935, Williams and Wilkins, Baltimore, page 129.

15. BLUMGART, H. L., LEVINE, S. A., and BERLIN, D. D.: Congestive heart failure and angina pectoris, Arch. Int. Med., 1933, li, 866–877.

SYMPTOMATIC PSYCHOSES IN PERNICIOUS ANEMIA *

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Although it has been recognized for many years that mental disturbances are frequently seen in association with pernicious anemia, the inclusion of organic psychoses among the important manifestations of the disease is rarely emphasized and seems insufficiently appreciated. Some of the early authors, among them Barrett [1] and Lurie,[2] stressed the fact that certain of the psychoses seen in pernicious anemia should be grouped with the organic mental illnesses rather than with the functional or psychogenic psychoses. Warburg and Jorgensen,[3] in a comprehensive discussion of the subject in 1928, came to the same conclusion. Only one recent writer, Hackfield,[4] considered that none of the psychoses seen in pernicious anemia were causally related to the physical disease.

The problem of psychoses accompanying pernicious anemia has apparently not been entirely ignored, but the careful differentiation of those psychoses which are an integral part of the organic disease from those which are merely coincidental has not received its due consideration. Many writers, including Smith,[5] Smithburn and Zerfas,[6] Ahrens,[7] Grinker,[8] and Goldhamer and collaborators,[9] have omitted any discussion of the psychiatric differential diagnosis entirely, and they have either merely enumerated the various mental symptoms observed, or they have grouped all the psychiatric disturbances under the general heading of "cerebral" or "psychic" symptoms.

The designation of symptomatic psychosis naturally implies an underlying physical disease, and such a psychosis is regarded as dependent upon an organic disturbance of cerebral function. The diagnosis of symptomatic psychosis is seldom difficult if its cardinal features are kept in mind. Kahn,[10] in a recent discussion of psychoses accompanying physical disease, restated that a disturbance of consciousness is the distinguishing feature of the psychiatric syndrome which has variously been termed symptomatic psychosis, toxic psychosis, delirium, or acute organic psychosis. The author discussed the complex clinical picture in some detail and pointed out how the primary disturbance of consciousness leads to confusion, disorientation, and defects in perception, registration and memory. The patient experiencing the disordered state of cerebral function may become irritable, depressed, delusional, or excited. It is emphasized that the disturbance of consciousness, manifested clinically in diverse ways, is the pathognomonic feature.

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It is not improbable that the symptomatic psychoses arising in pernicious anemia have been insufficiently recognized because, on the one hand, few internists have applied the established diagnostic criteria of psychiatry to the mental symptoms they have observed and, on the other hand, the psychiatrists have too often inadequately identified and described the associated anemia.

We wish to report three recently studied cases of classical Addisonian pernicious anemia personally observed by us in which the psychoses seem clearly to bear a symptomatic relationship to the deficiency disease.

Case Reports

Case 1. History: C. C., a white American spinster, aged 50, was admitted to the Psychiatric Clinic on July 8, 1933 with a referring diagnosis of tabo-paresis, made by a neuro-psychiatrist in private practice.

The ancestral stock, Irish and German, was made up of typically pyknic and extroverted individuals. The family had been remarkably long lived. The patient's father had been a heavy drinker and subject to wide swings of mood. He had been excessively irritable and had entertained unfounded suspicions and jealousies concerning his wife. One of the patient's sisters was moderately addicted to alcohol, and another was an inhibited "old-maidish" person. A third sister, aged 48, had been in a state hospital for the past 13 years with a diagnosis of psychosis with constitutional psychopathic inferiority.

The family had always been poor and had lived much within itself as a fairly harmonious group. Outside, religious, social or sexual interests were few.

The patient had been headstrong as a child and had left school at her own volition at the age of 12 in order to go to work. She had always been intellectually sluggish and disinterested, was deficient in common sense and dexterity, and displayed but little energy in her work and activities. She cultivated female friendships readily, but they were always shallow. Her family regarded her as a simple, submissive, and childish person. Although she manifested minor periodic mood swings, she was not given to brooding, exhibited no extraordinary emotional outbursts, expressed no feelings of inferiority or anxiety, and voiced no delusions or hallucinations. At 46 she passed through the menopause without any obvious physical or mental disturbances.

The present illness developed insidiously. During the year previous to admission the patient complained frequently of increasing fatigability. Progressive weakness ultimately rendered her incapable of assisting with housework, and eventually she could not walk the few blocks to attend church. She became forgetful, irritable, and nervous. Awkwardness in walking troubled her, and she was apt to fall if she stooped over, although no spasticity was observed. An exacerbation of all her symptoms followed the emotional disturbance occasioned by the sudden death of a brother three months before admission, and subsequently she became an invalid and made little attempt to help herself. The mental symptoms likewise progressed during the three months preceding admission. There was no weeping or obvious emotional depression, but she would sit staring ahead silently for long periods of time and seemed incapable of thinking clearly. At times her family thought her confused. No hallucinations or delusions were expressed. For a few days before admission she was incontinent of urine and feces, and complained of pain in her feet.

During the year of illness the patient had lost 25 pounds in weight, although her appetite had continued good. There had been no complaint of glossitis, stomatitis, or gastrointestinal disturbances, and no pains or paresthesias in the extremities. Neither had there been dyspnea or palpitation.

Physical Examination: The patient was poorly nourished, the skin had an icteric tint, and the mucosae were slightly pale. The pupils reacted normally to light and on accommodation. There was only slight papillary atrophy at the tongue margins. The teeth were unclean and extensively carious. The heart, lungs and abdomen were normal; neither liver nor spleen was felt. Neurological examination revealed sluggish superficial abdominal reflexes, questionable extensor responses on plantar stimulation, and absence of knee and ankle jerks. The deep tendon reflexes in the arms were normal, and the cranial nerves were intact. Sensory and cerebellar functions could not be tested because of lack of coöperation. The vital signs were normal; the blood pressure was 110 systolic and 85 diastolic.

Laboratory Findings: The red blood cells numbered 3,200,000 per cubic millimeter, and the hemoglobin was 10.9 grams (70 per cent Sahli). The white cell count was 10,500, with 85 per cent polymorphonuclear cells. There was marked anisocytosis and poikilocytosis of the red cells, with a notable excess of macrocytes. Actual measurement of 300 red cells after the method of Price-Jones, indicated a mean diameter of 9.5 micra, with a range of cell diameters between 4 and 13 micra. Platelets did not seem diminished in numbers in the blood smear. Gastric analysis showed no free hydrochloric acid even after the injection of 1 mg. of histamine. The stools were normal on several examinations, showing neither macroscopic nor occult blood, and giving no evidence of parasites or ova. The urine was normal. Complete fluoroscopic examination of the gastrointestinal tract disclosed no organic pathologic lesion. The blood Kahn test was negative, and the non-protein nitrogen was 58 milligrams per cent. Examination of the cerebrospinal fluid was negative.

Mental Status: On admission the patient lay quietly in bed. No abnormalities of the motor status were noticeable. Speech was normal at the sensorimotor level. She was apparently confused. From time to time she asked the nurse for a bed pan, but when it was brought she acted as if she did not know that it was there and appeared bewildered when questioned about it. She talked in a rather childish, colorless way. She was correctly oriented for place and person, but disoriented for time. When asked what month it was, she said, "June, ain't it? I can't think what month anyhow." The stream of speech was slow, but showed no intrinsic peculiarity. Her content of thought was poorly verbalized, but no delusions or hallucinations were expressed. Her attention was poor and fluctuated, but distractibility was not noteworthy. Her emotional tone was flat and colorless, although depression was not manifest. During the physical examination, however, she rolled around, groaned, and acted in a negativistic fashion. Memory was difficult to evaluate. When told the fox and grape fable, she could remember only that it was a story about some grapes. She refused to attempt the test for three minute retention. When asked the capital of Connecticut she said: "New Haven; I forget; I knew but I forgot again." In doing simple calculations, depression of memory was apparent, and it would take her some little time to arrive at the correct answer, but she seldom made any actual mistakes. Her general level of intelligence seemed dull, but this factor apparently did not account for her failures in tests of general information and memory. She had no insight into the nature of her illness.

On the basis of the physical examination, mental status, and laboratory findings, a diagnosis of pernicious anemia with symptomatic psychosis was made.

Since she refused to eat voluntarily, the patient was fed by stomach tube. The diet, high in calories, contained 300 grams of raw liver pulp daily, and included orange and tomato juice, cod liver oil, and brewer's yeast. In addition, 3 c.c. of Lederle's concentrated intra-muscular extract were administered twice weekly during the first month.

Although the characteristic response of reticulocytes to specific treatment was not observed, due probably to a complicating bronchopneumonia during the first week of treatment, a persistent reticulocytosis of 3 to 5 per cent was accompanied by a gradual

increase in the red blood cells, until at the end of five weeks the count was 4,200,000 and the hemoglobin 85 per cent (Sahli).

The mental and physical symptoms also improved steadily, and after 18 days on the gavage régime the patient began to take food voluntarily. The incontinence of urine and feces lasted only another week. At first she was frequently completely disoriented for time and place. She named not only the month but the year incorrectly, and she knew neither what sort of building she was in nor where it was. When questioned insistently concerning orientation, she seemed quite confused. On one occasion when told to eat her liver, since it was good for her, she thought the physician meant that she should eat her own liver, and she appeared frightened. This disorientation and confusion, however, cleared up after several weeks. Her emotional attitude, which in the beginning was childish, demanding, irritable, and uncoöperative, improved until she began to take pride in her returning strength and diminished irritability. Massage and exercise were frequently employed. At the onset it was necessary to urge her to undertake voluntary movement, but once she overcame her timidity, she exercised gleefully about the ward. The disturbances in memory likewise improved, although she never clearly recalled details of her first two weeks in the hospital. She was discharged October 14, 1933. At that time orientation was correct, and there was no confusion. She seemed a little stupid and still was afraid of blood tests, etc., and was obviously dependent on her sister's judgment. The knee jerks were normal, but she would not relax sufficiently to permit testing her ankle reflexes. Vibratory sense was absent below the iliac crests. Position sense also was greatly impaired in the feet and slightly diminished in the hands. The red blood count on dismissal was 4,400,000 with 90 per cent hemoglobin (Sahli).

Follow-Up: Under treatment with parenteral and oral liver general improvement continued during the next three months. Contact with the patient was lost during the year 1934, and when she was again seen early in 1935 it was reported that she had remained mentally and physically well. This was particularly interesting when it was learned that treatment had been changed to oral liver extract, 25 grams daily, on which the blood count had declined to 3,000,000 red cells and 50 per cent hemoglobin (Sahli). General physical, neurological, and mental examination revealed no changes since discharge from the hospital. Under more intensive liver therapy, supplemented with iron, the blood picture was again restored toward normal.

Case 2. History: M. T., a 50 year old Irish housewife, was sent by her family physician to the Psychiatric Clinic on November 17, 1934 because she had recently been expressing delusional ideas. Little information about the family history was obtainable, but an older sister was said to have died of pernicious anemia in 1923. The patient's husband and two adult daughters were entirely well. Her first child had died shortly after a difficult delivery; her fourth and last pregnancy, in 1916, had ended in a stillbirth.

The patient's personality was described as energetic and introverted. She made few friends, but these friends were very close to her. No mood swings had occurred. Sexual adaptation was normal. Details regarding the personality and general history were difficult to obtain because of the low intelligence of the informants. The family as a whole was ignorant and suspicious.

The patient's health had been excellent until the age of 34, when a diarrhea developed insidiously and continued intermittently for seven years. No details of this illness were recalled other than that there was an associated weakness and loss of weight. Recovery occurred spontaneously, and there had been no subsequent gastrointestinal symptoms. In recent years many abscessed and carious teeth had been extracted, and ultimately complete artificial dentures had been procured. An uneventful menopause occurred at the age of 45. The patient's dietetic habits had always been reasonable and moderate; she did not use alcohol. In the past three

years she had complained frequently of palpitation, but there had never been any cyanosis, peripheral edema, persistent cough, or unusual dyspnea.

During the early summer, about five months before admission, the patient developed an inordinate appetite for bananas, and she would often eat half a dozen in succession, without neglecting her usual diet. Her weight rose within a few weeks from her customary level of 115 pounds to 136 pounds. In spite of this apparent physical well-being, a personality change characterized by increasing irritability and emotional instability was apparent to her family. She was then taken to the mountains for a change of surroundings with the hope of averting a "nervous breakdown." While on vacation she began to lose weight and strength, and on returning home in September she looked tired and worn, and she weighed only 102 pounds.

About a month before admission she began to give evidence of outspoken mental abnormality. She accused her husband of having stolen one hundred and thirty dollars. When he denied it, she accused her niece of having taken the money and also ordered this girl, who was single, to leave the house because the patient thought she was pregnant. Furthermore, she accused her husband of being the father of the niece's illegitimate child, and of having a number of other clandestine affairs as well. She wept and cried a great deal. She insisted that her husband sleep in another room, and when he did, she was much upset and told him not to desert her. She slept poorly. She also accused her husband of having attempted to poison her food. Her family physician advised that she be sent to a psychiatric hospital.

Both the patient and her family denied that she had ever suffered soreness of the mouth or tongue, pain on swallowing, or indigestion or abdominal distress of any sort. Except for the diarrheal episode mentioned, the bowel function had always been considered normal. There was no recollection of distal paresthesias or tenderness or pains in the limbs, and no awkwardness of the hands or disturbances of sensation or gait. Nor had anyone detected any change in the patient's complexion.

Physical examination disclosed a scrawny, sallow-complexioned woman of pyknic physique with a sad expression and a tired demeanor. Although there was only moderate graying of the hair, she looked much older than her alleged 50 years. Her loose, dry skin had a lemon-yellow pallor, except for the soles and palms which were red. A profusion of telangiectases were scattered over the entire trunk, but none were found on the visible mucosae. Only moderate pallor was noted of the lips and nail beds. The sclerae were muddy, the irides blue-gray in color, and the lenses were slightly clouded. The teeth were replaced by well-fitting upper and lower dentures. The beefy red and deeply furrowed tongue looked abnormally large, and its edges and tip were atrophic; there were no ulcers, and the organ was not tender. The abdomen was normal, and neither liver nor spleen was felt. Muscle power in the extremities was moderately impaired. Complete neurological examination yielded nothing abnormal except serious impairment of vibration and position sense from the iliac crests distally. The vital signs were normal, with a blood pressure of 135 systolic and 95 diastolic.

Laboratory Studies: The red blood cell count on admission was 2,670,000 with 10.9 grams of hemoglobin (70 per cent Sahli). The white cells numbered 6,700 per cubic millimeter, of which 62 per cent were polymorphonuclear leukocytes and 30 per cent were lymphocytes. In the stained smear the red cells exhibited unusual variations in size and shape, with a definite predominance of very large, oval cells. The Price-Jones curve showed a mean red cell diameter of 8.74 micra, with a dispersion of cell diameters between 5 and 12 micra. The color index was computed to be 1.4. Platelets seemed diminished in numbers in the smear. The reticulocytes remained below 1 per cent for more than a week before effective specific therapy was instituted. By this time the red cell count had declined to 2,300,000. The color index was now 1.65. Since the Van Allen hematocrit indicated 24.5 c.c. of cells per 100 c.c. blood,

the volume index was computed at 1.24, and the saturation index 1.3 (Osgood-Haskins).

The urine gave a positive test for urobilin with Schlesinger's reagent on each of two analyses, but was otherwise normal. The stools were normal on several examinations. Gastric analysis revealed hyposecretion and absence of free hydrochloric acid even after the stimulation of ingested alcohol and injected histamine. Roentgenographic examination of the gastrointestinal tract indicated moderate dilatation and slight stasis in the first part of the duodenum, with a very questionable constriction in the descending loop. The Kahn test of the blood was negative, the icteric index was 7.0 and the non-protein nitrogen was 26 mg. per cent. The cerebrospinal fluid was normal in pressure, contained no cells, gave a negative test for globulin, and the Wassermann and colloidal benzoin reactions were negative.

Mental Status: On admission the patient was correctly oriented in all three spheres, and consciousness was clear. The next day, however, she stated repeatedly that it was 1932, and that she was in a private home. Speech was normal at the sensori-motor level, and the general motor status was not remarkable. She seemed somewhat sluggish, but no retardation of thinking was present. The stream of speech contained no intrinsic abnormalities. Attention and distractibility were within normal limits. There was an obvious, but loosely integrated paranoid trend. She said her husband was trying to kill her, that he had stolen money, and that he had done many cruel things to her at home. She believed that her food had been poisoned at home, and that "dope" was being put in it at the hospital. She thought the doctors were trying to kill her by draining her excessively of blood in doing blood counts. She was suspicious of every diagnostic test. She had no insight whatever into the fact that she was ill. She said there was no reason for her to be in the hospital, that all she needed was fresh air and that she had no anemia. Her emotional attitude was gloomy and pessimistic. At times brief weeping was observed. Her intelligence was rather dull as estimated from her grasp of general information. She would not coöperate in formal tests of calculation, and it was difficult to test her memory for the same reason. No impairment of recent memory was observed in casual conversation, but she did not recall events in the remote past very accurately.

On the basis of the physical examination, laboratory findings, and mental status, a diagnosis was made of pernicious anemia with symptomatic psychosis.

Course in Hospital: During the first two weeks of hospitalization the patient ran an elevation of temperature of one-half degree F. for which no cause was discovered, and the red cell count fell to 2,300,000. Effective therapy was then instituted, and the patient received daily intramuscular injections of 2 c.c. of extract derived from 10 grams of hog liver. A typical, pronounced reticulocyte shower began on the fifth day of treatment, reached its maximum on the seventh day, and was followed within 10 days by an increase in the red blood cells of 900,000 per cubic millimeter and a rise of 12 per cent in hemoglobin (Sahli). Four weeks later the red cell count had reached 4,100,000 and the hemoglobin was 90 per cent. Concomitant with this remission in the blood, the patient's general appearance improved, the glossitis disappeared, she ate better, and her strength increased, although there was no gain in weight.

Disorientation was never observed after the first week in the hospital. On several occasions during the first week of hospitalization brief periods of nocturnal confusion were observed, during which she wandered about looking for the bathroom, although she had used it on many occasions. In spite of the improvement in her physical condition and the disappearance of the mental organic symptoms, no improvement occurred in her delusional trend. She continued to be highly suspicious. She accused the nurses of sticking pins in her, said the physicians were poisoning her, and implied that the liver extract given her was dope. She would hide when physicians came on the ward, and was always apprehensive at night when the physician

and nurse entered her room while making rounds. She repeatedly said that cars passing by the hospital contained enemies. She claimed once that the nurses had phoned for a hearse to take her away. At no time, however, did she develop a systematized delusional trend. She was removed from the hospital against advice on January 5, 1935, seven weeks after admission, to continue under the care of her family physician.

Follow-Up: Ten weeks after discharge the patient was visited in her home. At that time her mental status was entirely normal, and apparently she had been sufficiently well to resume her usual household duties and responsibilities. She recalled the details of her hospitalization and said that her attitude had been foolish and unjustified.

It was learned that the patient had neglected all treatment for about six weeks after returning home, but at the insistence of her family she had, in the past month, returned to her physician and was receiving intramuscular injections of liver twice weekly. Shortly after this resumption of treatment her paranoid ideas and apprehensive attitude suddenly vanished. In spite of the lapse in treatment the patient had no complaints, she looked well, there was no glossitis, and she appeared to have gained in weight. However, her red blood cells numbered only 3,700,000 and her hemoglobin had fallen to 76 per cent (Sahli). The blood smear revealed slight macrocytosis with hypochromia. Supplementary treatment by the daily oral administration of iron was recommended.

Case 3. History: A. K., a 43 year old American housewife, was admitted to the Psychiatric Clinic on January 29, 1935 because she had developed delusional ideas while under treatment for pernicious anemia.

The ancestral stock was German. The family was said to have been characteristically of sturdy body build. The patient's mother had died at the age of 62 of an illness allegedly associated with anemia. There was no history of nervous or mental disease in the family. She had had four children, and they were living and well.

The developmental history was not noteworthy. The patient had first married at 16, and two years later she divorced her husband presumably because he had developed gonorrhea. Her second marriage, at 28, had continued entirely happy. She had renounced the Catholic church in remarrying.

The pre-psychotic personality showed no striking abnormality. Her chief interests lay in her home and family, and she was considered a competent housewife, friendly and pleasant. She was subject to short out-bursts of violent temper, but no mood swings were known to have occurred. The past medical history contained nothing of significance. She did not use alcohol habitually. Menstruation was still regular.

About 18 months before admission she began to fatigue easily, noted palpitation, and complained of vertigo and dyspnea on slight exertion. Her family physician diagnosed pernicious anemia, and she received specific treatment irregularly from that time on. When her symptoms were alleviated she was prone to discontinue treatment until the complaints returned with the ensuing relapse. At no time did she complain of soreness of the mouth or tongue, indigestion, abdominal pains, diarrhea, or distal paresthesias. Her condition took an abrupt turn for the worse three weeks before admission, at which time she suddenly became irritable and excited, and complained that people were talking about her. She maintained that the landlord and the neighbors upstairs were telling everybody that she had gonorrhea. She said that her husband was conspiring against her and was planning to do away with her. She became very dejected, suffered severe crying spells, and worried over what was to become of her. She often imagined that her sons were fighting among themselves and with the neighbors. During the few days just before hospitalization she would repeatedly call her physician on the telephone to be reassured that she did

not have gonorrhea. Her condition became so disturbing that the physician finally recommended her admission.

Physical Examination: There was a slight fever with a temperature of 100° F. by rectum. The patient was decidedly obese, weighing 170 pounds although only 62 inches in height. She was of a definitely pyknic body build. The hair was light brown, the eyes blue-gray, and the skin had a characteristic lemon tint. The sclerae were subicteric, and the mucous membranes were pale. There was no papillary atrophy of the tongue, and the organ was not reddened or sore. The heart was normal in size; the heart sounds were normal. There was no ascites, no dilatation of the abdominal veins, and no other signs of portal obstruction; the liver and spleen were not felt. Moderate pitting edema of feet and legs extended almost to the knees. No varicose veins were seen, and no focal tenderness, redness or swellings were noted. There was no lymphadenopathy. A complete neurological examination revealed absent knee and ankle jerks. The plantar reflexes were normal. Vibration sense was found impaired from the iliac crests distally, and was completely absent at the malleoli. There was slight awkwardness of the hands and fingers in attempting fine movements.

Laboratory Examinations: The red cell count of 1,950,000 was associated with 7.8 grams of hemoglobin (50 per cent Sahli). Of the 5500 white cells per cubic millimeter, 69 per cent were polymorphonuclears, and 30 per cent were lymphocytes. Platelets appeared to be reduced in numbers in the blood smear. Marked anisocytosis and poikilocytosis with conspicuous macrocytosis were confirmed by a Price-Jones curve revealing a mean red cell diameter of 8.23 micra with a dispersion of cell diameters between 5 and 12 micra. One normoblast and two megaloblasts were seen. Several urine analyses were negative except for the presence of urobilin. No free hydrochloric acid was found on gastric analysis even after the injection of histamine. The stool examination was negative. Lumbar puncture revealed normal cerebrospinal fluid. The blood Kahn was negative, the icteric index was 12, the total serum proteins were 6.10 grams per cent, and the non-protein nitrogen was 31 milligrams per cent. No organic lesion of the gastrointestinal tract was discovered by roentgenographic examination.

Mental Status: On admission, orientation was correct for place but fluctuated for time. A few hours after admission the patient thought she had been in the hospital two or three days, and she could not give the day of the week correctly. There was no other evidence of confusion. She was sluggish and inactive, but the motor status showed no other abnormality. Speech was normal at the sensori-motor level. The stream of speech was somewhat circumstantial. Thought processes were moderately retarded. Repeated fits of weeping were observed. She said, "I don't know why people should say things like that. Maybe I do have a disease. I don't know. Do you think I have?" Her delusional ideas were consistent with her depressed mood. She misinterpreted voices in the corridor and believed that people were talking about her. Memory for recent events was poor. This was not so evident on admission, but during her course in the hospital it was repeatedly demonstrated that she did not recall clearly details of events happening a few hours or days previously. She herself admitted that she could not think as clearly or recall things as readily as formerly. Her intelligence as judged by her general information seemed about normal. She was able to repeat fables and to recognize their significance satisfactorily. Memory for rote material was not good. She gave wrong answers in subtracting successive 7's without detecting the errors. She apparently had some insight into her condition. She knew she had pernicious anemia and that she was nervously ill, but insisted that if people would stop talking about her and let her alone, she would get over the nervousness. She did not believe her nervous state had any connection with mental disease.

On the basis of the physical examination, laboratory findings, and mental status, a diagnosis was made of pernicious anemia with symptomatic psychosis.

Course and Treatment: After a week of observation without specific treatment the patient was tried on an experimental parenteral liver extract for 12 days without improvement. Treatment was then changed to the oral administration of a commercial autolyzed liver extract. On this régime the blood picture showed a gradual improvement, and in 18 days the hemoglobin reached 82 per cent (Sahli) and the red cell count 2,910,000. This improvement was achieved in the face of a continued, unexplained fever of 1° F., and in the absence of the customary reticulocyte shower; the reticulocytes varied between 3 and 5 per cent throughout the period of daily observation. The psychotic manifestations showed no improvement. Depressive mood was at all times obvious, and the patient repeatedly expressed delusional ideas in keeping with the mood. At night panicky episodes would occur, during which she would leave her bed and wander into other patients' rooms, telling them that something dreadful was going to happen to her. She never became correctly oriented for time, and defective recent memory could always be demonstrated.

During the last week in February she complained of weak spells of abrupt onset and short duration. On March 1 she collapsed following a momentary attack of weakness and vertigo, and on this occasion she described a feeling of numbness beginning in the feet and extending upwards into the trunk. Her face was pale, the lips cyanotic, and the respirations slightly labored. Although the pulse felt weak, it was not rapid, and the blood pressure had not fallen. The episode passed off within a few minutes only to recur many times more during the following week. The patient recalled having had similar "fits" at intervals for two or three years. On March 10, during one of these attacks, she lost consciousness, the pulse and respirations ceased, and death ensued.

Necropsy by Drs. H. M. Zimmerman and D. M. Grayzel revealed an adipose subject with an abundance of yellow fat. The mucosa of the stomach was smooth and pink, and microscopically it appeared atrophic. The large, pale liver weighed 2345 grams; the spleen was also large and weighed 312 grams. Bone marrow taken from a vertebra and tibia showed hyperplasia and, in spite of recent liver treatment, the predominating cells were still megaloblasts, myelocytes, and erythroblasts. The red cells appeared distorted; very little fat tissue was present. Striking changes in the central nervous system included destruction of medullary nerve fibers and a reparative gliosis in the posterior columns and lateral pyramidal tracts of the spinal cord, as well as a degeneration of spinal ganglion cells. Definite nerve cell destruction was also apparent in the brain, especially in the frontal lobes.

A large, organizing thrombus was situated in the left femoral vein. The right pulmonary artery was completely occluded by a friable gray-brown clot, and several smaller branches of the left pulmonary artery were similarly plugged. A few small zones of infarcted tissue were found in the left lung.

Discussion

Our three cases resembled one another in that they all showed the fundamental symptoms of an organic psychosis. The first patient seemed confused on admission, and disorientation was observed on several occasions before improvement in the mental picture began. She was very easily fatigued, her attention was poor, and her intelligence was dull; but we did not feel that these features accounted for the disorientation and confusion. Memory seemed impaired at first but gradually improved, as did the other organic mental symptoms, under specific treatment.

In the second case, although the patient was clearly oriented on admission, disorientation for time and place was observed two days later as well as on several other occasions. Brief episodes of nocturnal confusion were observed, which we believed likewise indicated clouding of consciousness. Memory seemed poor but showed no striking change and was difficult to evaluate because of her limited intelligence. The defects in orientation and the episodic confusion improved under treatment.

The third patient was found to be definitely disoriented for time on a number of occasions, and recent memory defects were demonstrated repeatedly at times when her attention and coöperation were satisfactory. No improvement in the symptoms occurred during two weeks of specific treatment, after which her death from a pulmonary complication terminated our observations.

The opinion of the psychiatric staff was unanimously in favor of a diagnosis of symptomatic psychosis in all three cases on the basis of the organic symptoms we have just discussed. It was recognized, however, that the content of the psychosis and the affective symptoms in each case could be understood only in terms of the total personality and its way of experiencing.

The first patient was a middle-aged spinster of low intelligence who always had been childishly dependent upon her family. During her illness her helplessness became exaggerated. She demanded attention from the nurses and constantly called upon her sisters for advice and sympathy. At first she refused to coöperate with treatment and even induced vomiting deliberately. She was timid and was afraid to try to walk after her strength began to return, so that it was necessary to handle her firmly, as one would a refractory child. Eventually, however, she took a childish delight in her recovery. No affective depression ever was seen, and no hallucinations or delusions were elicited. The picture superficially resembled an extreme invalid reaction of the so-called neurasthenic type in a person of low intelligence; but we felt that the additional confusion and disorientation indicated the correct diagnosis of symptomatic psychosis.

The clinical picture in the second case resembled agitated depression. Little reliable information was obtained concerning the patient's prepsychotic personality, so that it was difficult to interpret the content of the psychosis in terms of previous experience. She manifested the extreme suspiciousness and vague paranoid trend described by Barrett [1] in his cases. The organic mental symptoms improved under specific treatment, but the affective depression and paranoid trend did not improve, which is not surprising since these symptoms really are personality manifestations and not organic cerebral symptoms. The paranoid depression cleared quite suddenly and without any apparent reason after discharge.

The third patient was obviously depressed and expressed paranoid ideas in keeping with her depressed mood. The delusional content of the psychosis was understandable in terms of her past experience. The disorienta-

tion for time and memory defects were definite, however, so that we believed that symptomatic psychosis was the correct diagnosis although the picture in other respects was not distinguishable from manic depressive psychosis.

It is interesting to review briefly the relationship between the physical and mental disturbances in these cases. In our first case a symptomatic psychosis was present when the erythrocyte count was 3,200,000 per cubic millimeter. We did not believe that this degree of anemia was in itself sufficient to produce a psychosis. Furthermore, although the mental disturbance improved under treatment while the erythrocyte count was rising, no mental symptoms were present 18 months later when the red cell count had fallen to 3,500,000 per cubic millimeter due to insufficient treatment. In the second case also the organic mental symptoms disappeared while the anemia was responding to treatment, and did not reappear even though the erythrocyte count fell from 4,100,000 to 3,700,000 when treatment was discontinued temporarily. The delusional trend in this case apparently was not affected by treatment, but as we have mentioned above, we consider delusions as personality manifestations and not as organic cerebral symptoms. The third patient died before we were able to study the relation of the symptomatic psychosis to the anemia.

It is apparent that in our cases the character and severity of the mental disturbances bore no consistent relationship either to the degree of anemia or to the extent of the neurologic manifestations. While this on first thought may appear implausible, it seems to us fully as admissible as the analogous, well-established observation that neurologic involvement varies quite independently of the state of the blood; subacute combined sclerosis sometimes appearing long before the actual development of anemia. Goldhamer et al.[9] on the basis of wide experience also have observed that cerebral manifestations may occur either alone or in association with cord disturbance, that they may be present with or without evidence of anemia, and that they may present themselves as the earliest and only manifestations of pernicious anemia.

Summary of Cases

1. C. C., a spinster of 50, with a family history of mental disease, had been ill one year with insidious development of symptoms of anemia, followed after a few months by gait abnormality and mental disturbances. Exacerbation of symptoms by a severe emotional upset led to physical invalidism and precipitated a frank psychosis with confusion, disorientation and memory defect; no insight. Neurological signs of advanced dorsal column degeneration affecting the legs, atrophic glossitis, and achlorhydria were found. Hyperchromic, macrocytic anemia of moderate degree responded well to liver therapy, as did the mental and neurological symptoms. During the ensuing two years the mental and physical improvement was

well maintained in spite of moderate fluctuations in the anemia due to irregular treatment.

2. M. T., aged 50, housewife, had a family history of pernicious anemia. A seven year episode of diarrhea occurred in early adult life. She was ill five months with irritability and emotional instability followed by rapid decline of weight and strength, the late appearance of outspoken mental abnormality with paranoid delusions and fluctuating disorientation and confusion; no insight. Emaciation, glossitis, and signs of advanced dorsal column degeneration were associated with a moderately severe hyperchromic, macrocytic anemia as well as urobilinuria and achlorhydria. Liver therapy evoked a typical hematopoietic response, with rapid remission of anemia, improvement in general well-being, and early disappearance of disorientation and confusion. Paranoid ideas persisted two months longer and then vanished in spite of temporarily irregular and inadequate liver therapy.

3. A. K., housewife of 43, had been diagnosed pernicious anemia two years previously but had accepted liver therapy irregularly and inadequately, with resultant exacerbations and therapeutic remissions. Three weeks before admission she suffered abrupt onset of irritability and excitement with disorientation, memory impairment, depression, and delusional ideas; little or no insight. The patient was obese, with a sub-icteric pallor, and pitting edema of the legs. Neurological signs indicated early dorsal column degeneration. Severe hyperchromic, macrocytic anemia with leukopenia was associated with achlorhydria and slight bilirubinemia. Incomplete therapeutic remission, readily induced under liver therapy, was accompanied by no physical or mental improvement, and was terminated by sudden death with pulmonary embolism. Necropsy revealed degenerative lesions of the brain and spinal cord, atrophy of the gastric mucosa, enlargement of the liver and spleen, and a megaloblastic bone marrow with hyperplasia.

Summary

1. Three cases of pernicious anemia with symptomatic psychosis are described.

2. None of the patients had shown indication of organic mental disturbance before the development of pernicious anemia.

3. In all three cases symptoms indicating an organic disturbance of cerebral function were observed.

4. In all three patients additional symptoms occurred which were related to previous experience and ways of reacting to the environment rather than to organic cerebral disturbance.

5. Two of the patients were obviously depressed and paranoid.

6. The organic mental symptoms responded to specific treatment in two cases. The third patient died of pulmonary embolism before adequate treatment had been given.

7. None of the patients showed evidence of severe subacute combined sclerosis.

8. There was no apparent relationship between the degree of anemia, the severity of the psychosis, and the extent of neurologic manifestations.

REFERENCES

1. Barrett, A. M.: Mental disorders and cerebral lesions associated with pernicious anemia, Am. Jr. Insanity, 1913, lxix, 1067–1078.
2. Lurie, L. A.: Pernicious anemia with mental symptoms, Arch. Neurol. and Psych., 1919, ii, 67–109.
3. Warburg, E. J., and Jorgensen, S.: Psychoses and neurastheniae associated with achylia gastrica and megalocytosis, and the relation between this syndrome and pernicious anemia. (*a*) Psychoses, Acta med. Scandinav., 1928, lxix, 537–592. (*b*) Neurastheniae. Remarks on the diagnostic form of color and volume indices, Acta med. Scandinav., 1929, lxx, 193–215.
4. Hackfield, A. W.: Studies of the etiological relationship between the somatic and psychotic disturbances in pernicious anemia; a critical review, Jr. Nerv. and Ment. Dis., 1932, lxxvi, 31–48.
5. Smith, L. H.: Mental and neurologic changes in pernicious anemia, Arch. Neurol. and Psych., 1929, xxii, 551–557.
6. Smithburn, K. C., and Zerfas, L. G.: The neurological symptoms and signs in pernicious anemia, Arch. Neurol. and Psych., 1931, xxv, 1100–1110.
7. Ahrens, R. S.: Neurologic aspects of primary anemia, Arch. Neurol. and Psych., 1932, xxviii, 92–109.
8. Grinker, R. R., and Kandel, E.: Pernicious anemia; results of treatment of the neurologic complications, Arch. Int. Med., 1934, liv, 851–871.
9. Goldhamer, S. M., Bethell, F. H., Isaacs, R., and Sturgis, C. C.: The occurrence and treatment of neurologic changes in pernicious anemia, Jr. Am. Med. Assoc., 1934, ciii, 1663–1667.
10. Kahn, E.: Psychoses complicating other diseases, Yale Jr. Biol. and Med., 1935, vii, 215–223.

OLEOTHORAX: CLINICAL AND EXPERIMENTAL *

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Therapeutic pneumothorax is being used more and more in the modern treatment of pulmonary tuberculosis. During the course of collapse-treatment various difficulties and complications may occur. The lung may reëxpand prematurely, especially when adhesions are present and when the organ is held under partial compression. On the other hand, it may be impossible for the lung to unfold on account of dense fibrosis in it and in the pleura at a time when the disease is considered healed. Loss of elasticity as a result of the development of a large amount of fibrous tissue around a cavity may prevent its closure in spite of elevation of intrapleural gas pressure. A very mobile mediastinum may be bowed over toward the opposite side, so that increased amounts of gas introduced enlarge the pleural space instead of having the desired effect of permitting further collapse of the lung. Tuberculous empyema may develop and persist for many months, leading to expansion of the lung and debilitation of the patient. In certain patients all of these difficulties can be overcome by replacing the gas in the pleural cavity with oil.

Oil is an irritant to the pleura resulting in thickening and fibrosis. Due to its incompressibility and its weight it maintains a better collapse than does air, the latter allowing some expansion with each inspiration. How the presence of oil minimizes the formation of pleural exudate is in doubt, but it may be related to the surface tension of the oil. Although both olive oil and gomenolated paraffin oil have been shown to affect the acid-fastness and ability of growth of tubercle bacilli in vitro,[1] normally staining bacilli have been seen in the pleural effusions developing under oil. The beneficent effect of oleothorax on tuberculous empyema may not be due to direct action on the bacillus but to stimulation of the reactive cells of the body. The slow absorbability of oil has certain advantages. But its irritating quality and the dense shadow it casts over the shadow of the lung in the roentgen-ray film are occasional disadvantages. Its worst feature is the damage it can do to the lung when it leaks into that organ.[2]

Paraffin, or mineral, oil is used when one desires prolonged collapse without the necessity of many refills. It is also employed by some to prevent the reformation of pus; others prefer vegetable oil for this purpose. Olive, cotton seed, corn, rape seed, and poppy oils have all been used in the pleural cavity. A difference of opinion exists as to whether vegetable oil is less irritating than mineral oil.[3] The latter is more stable and does not become hydrolyzed or rancid, a change which must be avoided when using

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vegetable oil. Virgin olive oil is more neutral than that obtained from later pressings of the olive.

The conflicting views as to which is the more irritating to the pleura, mineral oil or olive oil, are based on both clinical and experimental observations. Matson [4] and Kuss,[5] for instance, find paraffin oil milder than olive oil in its action on the human pleura, and my own experiments on rabbits show no real difference in their irritative qualities. These opinions, I believe, differ from those held by most workers. Some believe that the effect of oil is due principally to its mechanical action; some that its modus operandi is through irritation of the pleura, and some believe it has an irritant action on the lung. Those who believe in its irritative effect seek a marked pleural reaction by giving large doses of oil at the first filling [6]; or, eschewing compressive action, use only negative intrapleural pressures, and recommend not filling the pleural space with oil as its weight is not necessary to close a pulmonary cavity.[7] To complicate the problem still more there is the question as to whether it is better to use vegetable oil—because it is absorbed into the lung more quickly and more completely than is mineral oil. Several experimenters have found that the lung reacts quite markedly to absorbed oil.[8] This may be beneficial when one desires a stimulation of fibrosis to close a cavity, but it may exercise a deleterious effect on re-expansion. Regarding the effect of oil on pleural pus, Ross and Tulloch would choose olive oil on the grounds that the higher the acid content the greater the lethal effect on tubercle bacilli (acid value of paraffin oil zero, of neutral olive oil 0.07 per cent). It is, therefore, evident that definitive conclusions have not been reached regarding what oil to use and even, for special indications, whether oil is as useful as gelatin for empyema [9] or as salt solution for compression.[10]

Gomenol, an aromatic oil, is frequently added to oil when it is injected to control tuberculous empyema. Its antiseptic action is rather feeble and some operators do not use it at all. Injected in full strength into the uninfected pleural cavity of the rabbit it causes an intense reaction and the animal dies within 24 hours.[11] Several patients have exhibited general reactions which seemed to indicate a toxic effect of gomenol (Matson, Bernou, Serio [12]). Probably not more than a 10 per cent dilution of gomenol in the chosen oil should be employed. Good results have been obtained with metaphen, and the Germans generally use iodipin.

Experimental Oleothorax

The various oils injected into the pleural cavity of the laboratory animals cause quite similar reactions. Tuberculous pleurisy is difficult to obtain experimentally and most of the experiments have been performed on uninfected animals, some on animals with pulmonary disease. Early reports on such experiments showed that the injected oil led to the development of extensive pleural adhesions; though, in patients, oleothorax has been successfully employed to combat this very condition. Oil injected into the

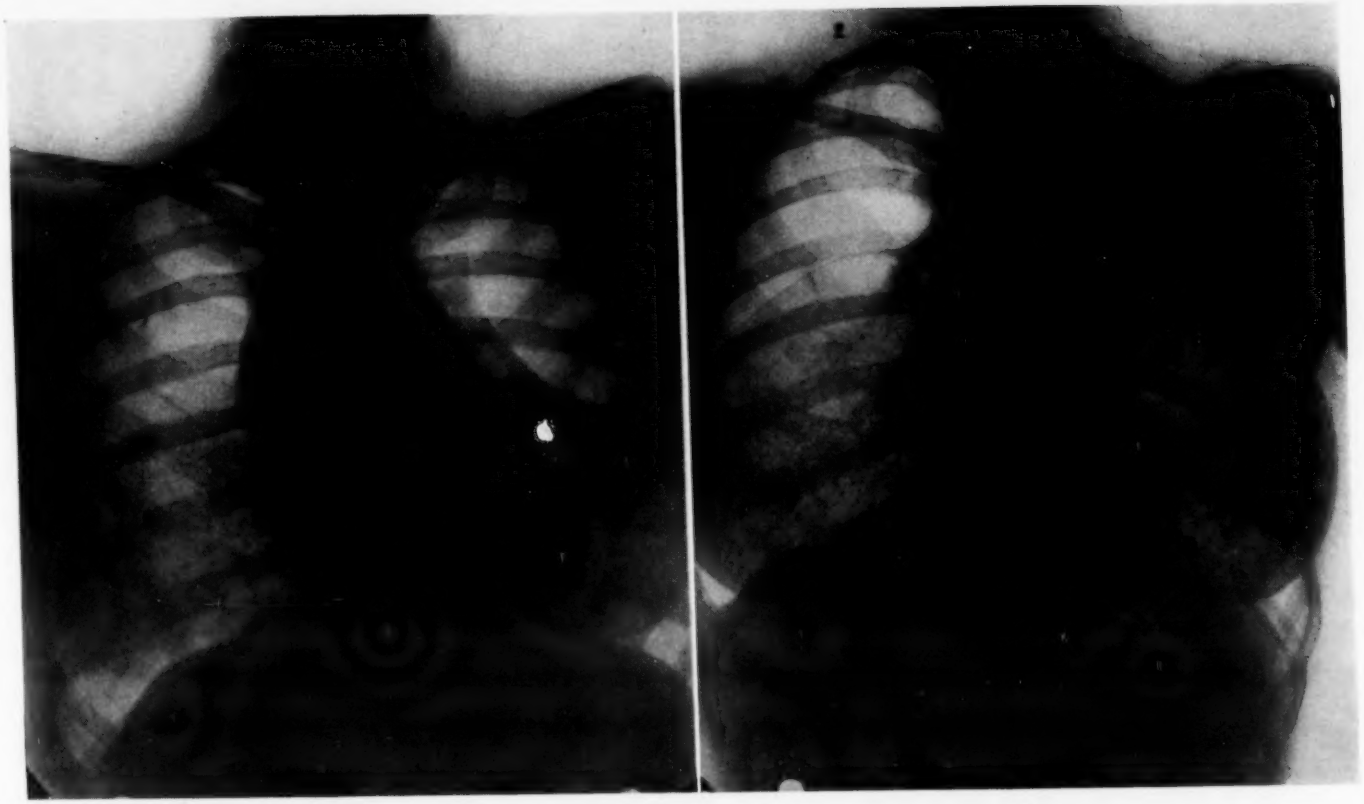
virgin pleura frequently causes the formation of an exudate. This effect may be valuable in the human case when one wants to thicken and stabilize a movable mediastinum. Congestion of the pleura is an early reaction and small hemorrhages are not at all uncommon. The membrane becomes infiltrated with pus cells and clasmatocytes, the latter phagocyting the oil and appearing as large " foam " cells and giant cells. Fibrin is deposited into and on the pleura and organization of the infiltrated and fibrinous tissue soon leads to fibrosis. Vegetable oil becomes emulsified and is carried into the lung by way of the dilated lymphatics and in phagocytic cells.[13] Some of it undergoes lipolytic action here,[14] and some in very finely dispersed droplets is carried away in the circulating blood and can be found in various organs.[15] The absorption of vegetable oils is much more rapid than that of mineral oil. The thickened pleural membranes become adherent. Bettini finds that the reaction of the lung to the presence of absorbed oil causes a fine pulmonary fibrosis; this may be a factor in healing our human cases.

Indications for Oleothorax

The principal actions of oil blockage are mechanical, irritative and antiseptic.

(*a*) *Antisymphysis.* When the collapsed lung reëxpands prematurely, that is, before the disease process for which pneumothorax has been given has healed, all the benefit previously gained is threatened. When the lung attaches itself to the diaphragm, creeps out along it and begins to ascend the thoracic wall, even increased intrapleural gas pressures may not prevent further unfolding of the organ. Usually the tuberculous lesions are in the upper third of the lung; before this portion has reëxpanded and while there is still a good selective collapse of this diseased part, only the base being attached to the parietal wall, the gas in the pneumothorax pocket may advantageously be replaced with plain paraffin oil. (Figure 1.)

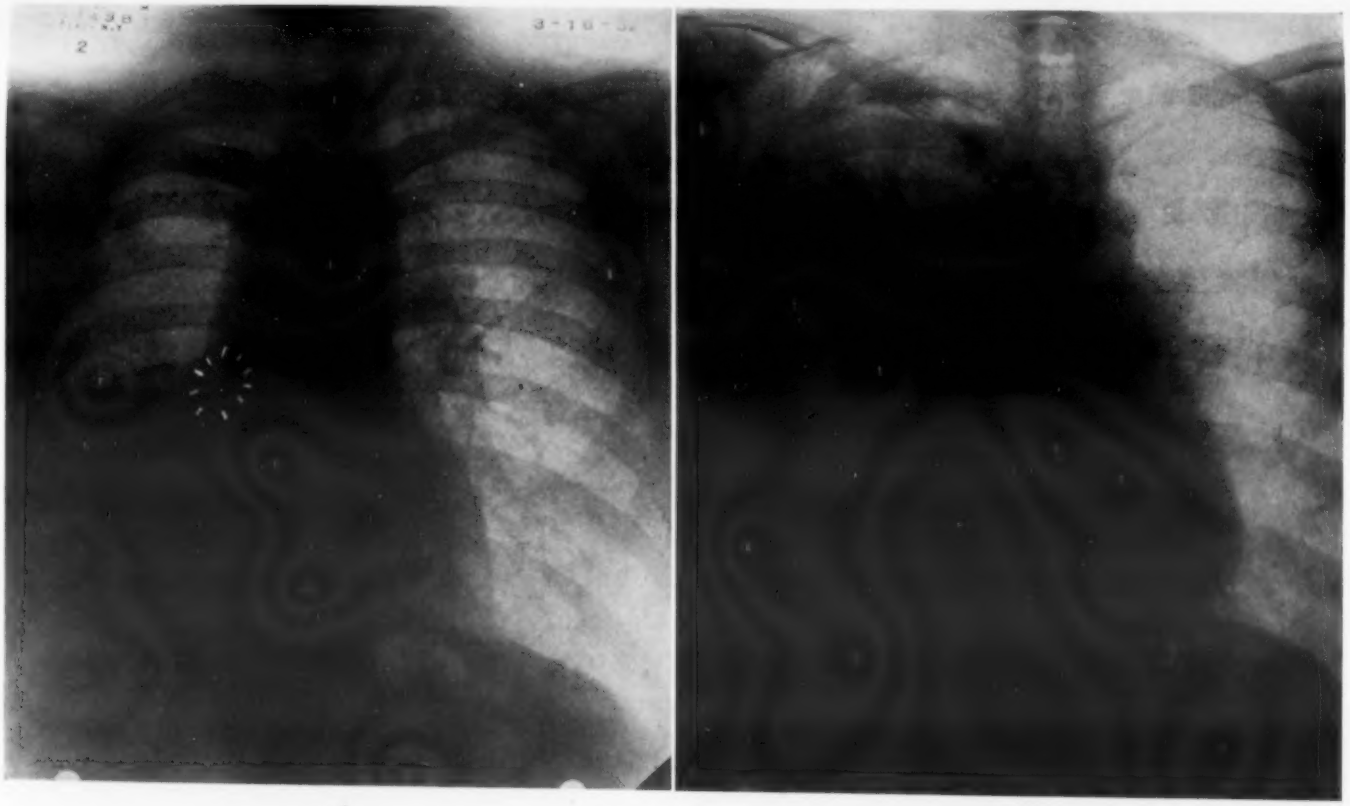
(*b*) *Compressive.* Adhesions may act as guy-ropes, pulling on a relaxed lung and preventing collapse of a cavity. If it is impossible to sever the adhesions or to stretch them out by increasing gas pressures, oleothorax or thoracoplasty must be considered. The latter may be impossible on account of the state of the opposite lung or the general condition of the patient. If the cavity is not too peripheral and if oil pressure can be exerted on the lung surrounding it, the pleural pocket is filled with oil and by repeated injections its pressure is gradually increased in an effort to close the cavity.[16] When the cavity-bearing apex is widely and diffusely adherent, little good can be expected. But if the oleothorax is anterior, the lung being squeezed into the posterior gutter, the chances of success are improved. Some think that oil under pressure is too great a hazard because if a large amount should burst into the lung it might cause suffocation or oil pneumonia. Under the circumstances mentioned above, i.e., an ineffective pneumothorax and surgical means contraindicated or impossible, and with



A *B*

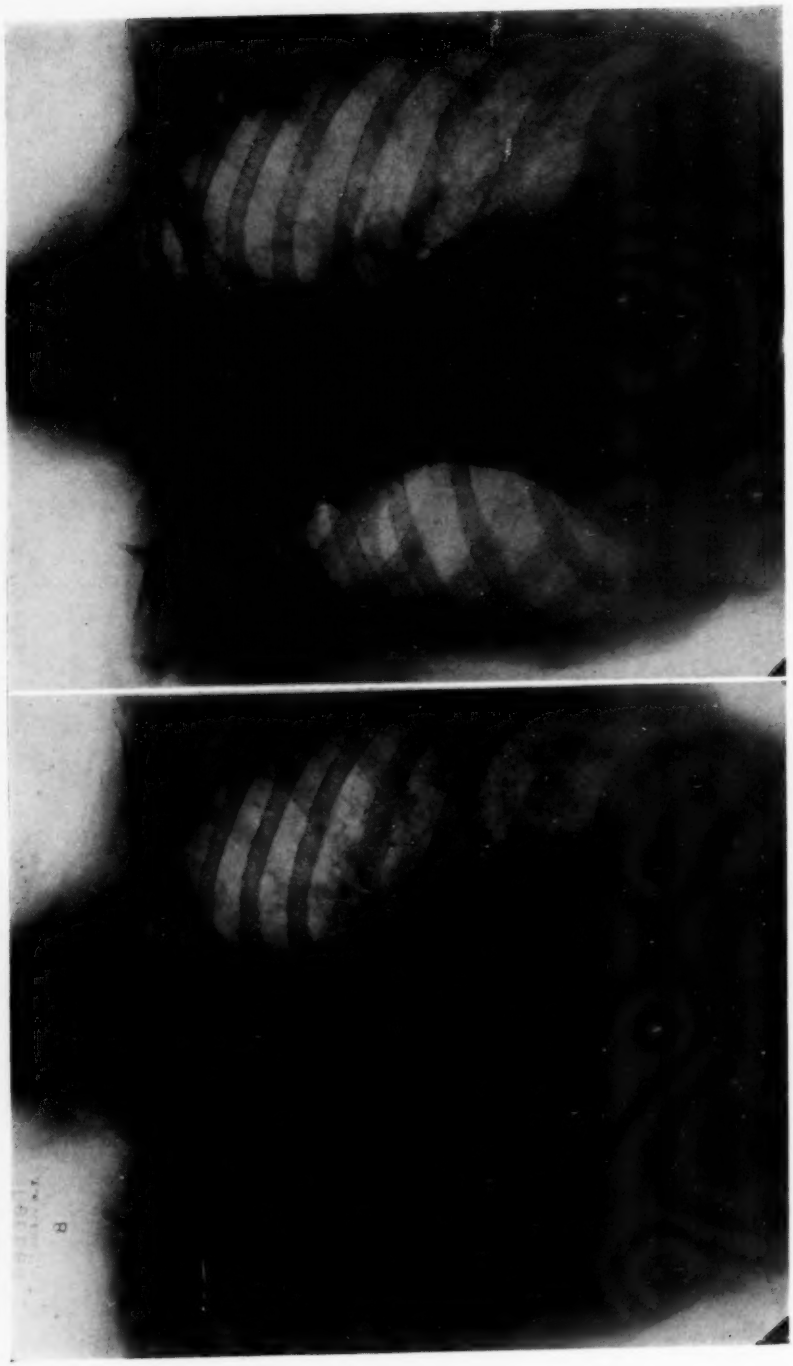
FIG. 1. (*A*) M.K. April 24, 1931. Artificial pneumothorax on left since March 1930. Uncollapsed cavity at third rib. Pneumothorax on right since November 1930.
(*B*) June 2, 1933. Cavity may be present on the left as tubercle bacilli are occasionally present. General condition excellent.

mothorax on right since November 1930.
(*B*) June 2, 1933. Cavity may be present on the left as tubercle bacilli are occasionally present. General condition excellent.



A *B*

FIG. 2. (*A*) I.B. March 16, 1932. Artificial pneumothorax March 1930; multiple cavities; phrenic January 1931; pleural effusion summer 1931. Film shows outlined cavity with base expanded. Oleothorax begun April 1932.
(*B*) February 6, 1933. Removal of fluid later shows no cavity at the base.



B

A

FIG. 3. (*A*) D.O. Oleothorax for tuberculous empyema.
(*B*) Appearance of lung after aspiration of oil. Lung did not expand; it merely retracted to right.

the cavity not too peripheral, oleothorax is indicated. Kuss thinks that high oil pressure is less dangerous than the fluctuating pressure of hypertensive pneumothorax. (Figure 2.)

(*c*) *Antiseptic.* When tuberculous empyema develops and the pus continues to reform in spite of repeated aspirations and irrigations of the pleural sac, the remarkable drying-up action of oleothorax is most satisfactory. (Figure 3.) Pleural lavage should always be tried first. When the empyema is causing grave symptoms, oil has a definite detoxifying action, an effect not unexpected after Clerc's experiments on the neutralizing action of gomenolized oil on various exotoxins, the blocking of lymphatics and its inhibitory action on acid-fast organisms. Even if the pus reforms, the improvement in the patient's condition may prepare him for collapsing operations which he could never withstand during the early period of grave tuberculous empyema. Dumarest [17] and Bernou warn that oleothorax is contraindicated in malignant tuberculous pyothorax because little benefit can be expected and time is lost before more radical operations. Some patients have been cured, nevertheless.[18] Primary tuberculous empyema, i.e., occurring without previous therapeutic pneumothorax, yields very excellent results with this treatment. Some cases of mixed infection by tubercle bacilli and other organisms have been cured with oleothorax but better antiseptics are available; if oleothorax is employed the use of 20 per cent gomenol in oil is recommended.

(*d*) Sometimes after sufficiently prolonged pneumothorax, the lung has become so fibrous or is so bound by an unyielding pleura that it will not reexpand. If air refills are stopped, the lung is drawn toward the thoracic wall which becomes greatly retracted and the mediastinal organs are drawn over and perhaps twisted. Circulatory symptoms and pain or discomfort from the increased negative pressure sometimes result. The onset of this distress becomes evident before the lung has reached the chest wall. To correct this the operator may choose permanent pneumothorax, oleothorax or thoracoplasty. In some cases oleothorax is best.

(*e*) *Bronchopleural Fistula.* If the perforation is large, or low in the pleural cavity, oleothorax is contraindicated. In fact, many operators refuse oil treatment to any fistulous patient. The best indication is said to be suffocating pneumothorax with valvular fistula if attacks recur.[19] Bernou [20] well expresses the limitations of the use of oleothorax in pulmonary perforation and advises against it when a number of adhesions hold the cavity open, when the perforation connects a cavity with the pleural space or when the pleura is thick and the parenchyma dense. He admits its usefulness when the pleura is supple and free of adhesions and the lung perfectly compressible. These conditions must seldom occur except when pulmonary perforation is due to a needle wound which nearly always heals unaided. Some successes have been reported when the opening through pleura into lung is minute and intermittent. A very good estimation of its size can be made from various signs. The pleural cavity is not filled

FIG. 3. (*A*) D.O. Oleothorax for tuberculous empyema. (*B*) Appearance of lung after aspiration of oil. Lung did not expand; it merely retracted to right.

with oil as in the conditions mentioned earlier but the oil level is kept below the level of the fistula, as determined by the usual position of the patient.

(*f*) *Mediastinal Relaxation.* This may interfere with collapse of a pulmonary cavity and can be corrected by instilling a small amount of oil which usually causes a pleural exudate with resultant thickening and fixation of the yielding membrane. Air pressures are then exerted against the lung rather than against a mobile mediastinum.

(*g*) Other rare and not generally accepted indications have been offered: to avoid air refill reactions, to maintain collapse when it is impossible or inconvenient for the patient to go for refills frequently, etc. Oleothorax demands as much supervision as does pneumothorax treatment and the patient should be under observation. Small amounts of oil have been injected along with the first few air refills to decrease the number of serous effusions of pneumothorax.[21] Unverricht's [22] results were decidedly good, those of Heise [23] fair.

(*h*) *Non-Tuberculous Diseases.* Oleothorax has been used to supplement therapeutic pneumothorax in bronchiectasis. Some successes have been reported in acute pyogenic empyema, and in chronic empyema when the lung fails to expand and decortication is dangerous because of preexisting bronchopleural fistula.[24]

Technic

Without going into many details the institution and conduct of treatment are based upon experience with collapse therapy. It is usual to test the response of the pleura to small doses of oil injected during an ordinary refill of air, gradually increasing the doses until the pleural cavity has been filled. Except in compressive oleothorax the oil pressure is left lower than atmospheric pressure. The need of a refill is determined from the return of symptoms and by puncture rather than from roentgenologic evidence. Refills may be indicated after a month or two up to a year or more. Mineral oil is absorbed much more slowly than is vegetable oil. The latter is chosen, therefore, by some for treating empyema in the belief that the antiseptic dissolved in it acts more effectively. Unless it is desirable to maintain the oleothorax permanently (as when thoracoplasty is contraindicated or refused), the oil is removed when the purpose for which it has been given has been accomplished. Pneumothorax is then resumed because it is easier to control collapse and reëxpansion than with oleothorax.

Complications

With the first injections, especially into an uninfected pleura and even when a few c.c. of oil are used, pleurisy with effusion may occur. The reaction may be severe and the effusion may become purulent. Pleurisy may develop when the chest is full of oil, causing a high pressure which may prove dangerous. Perforation of the lung is the accident which is

most feared. Many of the bronchopleural fistulae discovered during oleothorax are not due to the oil but were present previously and are revealed by the patient's tasting gomenol whose aromatic quality permits its odor to seep through a very small opening which may open and close intermittently. Flooding of the lung with oil may cause death from suffocation. When oil escapes into the thoracic wall through careless technic or from ulceration, a painful and persistent paraffinoma results. With good judgment in the choice of patients and careful technic in giving the treatment, however, serious complications are uncommon.

Results

The table below shows some of the results obtained. They are really

OLEOTHORAX
Results

Indication	Tbc. Pyothorax	Anti-Symphysis	Compressive	Bronchial Fistula
270 cases (8 authors)[25]	139	94	37	36
Per cent satisfactory	74	71	54	39
		alone or combined		
Matson,[26] 100 cases	50	50		
Per cent satisfactory	60	50		
		Complications Per cent (Matson)		
Pur. effusion	12 recurred	10		
Bronchial fistula	10	6		
Cutaneous fistula	10	4		
Paraffinoma	0	12		

good when one considers that many of these patients would not have been acceptable for radical thoracic operations and that oleothorax is substituted for pneumothorax when the benefit derived from the latter is threatened or in real jeopardy. The best results are those obtained with "cold," or mild, tuberculous empyema which is not responding to the usual treatment, aspiration and lavage of the pleural cavity, and with prematurely reëxpanding lungs especially when the latter are selectively collapsed. Pyothorax in this table includes both mild and grave cases. Matson's results are given separately as being the best and largest series in American literature. Matson's figures show that there is frequently more than one indication in any one patient, for the use of oleothorax. Forty per cent of closures of bronchopleural fistulae seems remarkably high. I have not had a single success.

BIBLIOGRAPHY

1. Clerc, J.: À propos de l'oléothorax. Étude bactériologique et experimentale du goménol, Rev. de la tuberc., 1930, xi, 39–75.
   Morel, A., and Rochaix, A.: Sur le pouvoir infertilisant de quelques essences végétales vis-à-vis de divers microbes pathogènes, Compt. rend. Soc. de biol., 1927, 1311. Recherches comparatives sur l'action microbicide des vapeurs de quelques essences végétales, Ibid., 1921, lxxxv, 861–863.
   Courmant, P., Morel, A., and Bay, I.: Sur le pouvoir infertilisant de quelques essences végétales vis-à-vis du bacille tuberculeux humain in vitro, Compt. rend. Soc. de biol., 1927, xcvi, 1313. Sur le pouvoir infertilisant de quelques essences végétales et de leurs constituants, vis-à-vis des cultures homogènes de bacille tuberculeux humain, Ibid., 1928, xcviii, 318–320.
   Kolmer, J. A.: Bronchial disinfection and immunization; effects in rabbits of intrabronchial injections of various chemical disinfectants, Arch. Int. Med., 1933, li, 346–366.
   Tulloch, W. J., and others: Bacteriological characteristics of 100 strains of tubercle bacilli isolated from sputum, Tubercle, 1924, vi, 105–123.
   Tulloch, W. J.: Preliminary report of experimental immunization against tuberculosis in guinea pig by use of "oleovaccine," Tubercle, 1926, vii, 218–220.
   Tulloch, W. J., and Ross, G. R.: Further observations upon tuberculosis inoculata of guinea pig, Tubercle, 1926, vii, 265–276, 321–332.
   Waitz, C.: Experimentelles zum Oleothorax, Beitr. z. Klin. d. Tuberk., 1930, lxxiii, 59–72.
2. Hayes, J. N.: Dangers and complications of oleothorax, Jr. Thorac. Surg., 1932, ii, 34–43.
3. Saley, D. H., Willis, H. S., and Ellwart, L.: Studies in experimental oleothorax, Trans. Nat. Tuberc. Assoc., 1934, 141–145.
   Waitz, C.: See reference 1.
   Goldenberg, I., and Flanchik, S. I.: Superiority of mineral oil over olive oil in oleothorax, Am. Rev. Tuberc., 1932, xxvi, 754–762.
   Bettini, D.: Ricerche sperimentali sull' oleotorace, Riv. di pat. e clin. d. tuberc., 1933, vii, 400–419.
   Ballon, H.: Some experiences with oleothorax, Am. Jr. Surg., 1932, xvi, 1–11.
   Archibald, E.: Note on compression of lung by paraffin oil in pleural cavity, Am. Rev. Tuberc., 1922, vi, 898–899.
4. Matson, R. W.: Oleothorax, Am. Rev. Tuberc., 1932, xxv, 419–468.
5. Kuss, M. G.: Technique des oléothorax, Rev. de la tuberc., 1926, vii, 100–116.
6. Courtois, R., and Bonamis, P.: Pleurésies provoquées et injections massives en plèvre saine d'huile goménolée, Rev. de la tuberc., 1934, ii, 955–980.
   Guinard, U.: Rev. de la Tuberc., 1933, 84–87.
7. Morin, J., and Bouessée, F.: À propos de l'oléothorax, Ann. de Méd., 1929, xxv, 331–350.
8. Waitz, C.: See reference 1.
   Bettini, D.: See reference 3.
9. Hunter, R. A.: Gelatinothorax, Tubercle, 1931, xii, 204–206.
10. Triboulet, and Sors, M.: Essais de sérothorax, Rev. de la tuberc., 1933, i, 74–87.
11. Personal experiments.
12. Matson, R. W.: See reference 4.
    Serio, F.: Incidenti da oleotorace, Rif. med., 1931, xlvii, 835–837.
13. Binet, L., and Verne, J.: Sur l'absorption de l'huile par la plèvre, Compt. rend. Soc. d. biol., 1924, xcl, 66–68. Les processes histologiques de l'absorption des graisses par la plèvre, Bull. d'histol. appliq. à la physiol., 1925, ii, 14–190. (Also in Ann. d'anat. pathol. méd.-chir., 1925, ii, 97–104.)
14. Bratiano, S., and Bratiano, C.: L'absorption des graisses animales par la plèvre, Bull. d'histol. appliq. à la physiol., 1928, v, 133–145.

15. BETTINI, D.: See reference 3.
16. KUSS, M. G.: Rapport sur l'oléothorax, Rev. de la tuberc., 1928, ix, 714–741.
17. DUMAREST, F.: Indications for oleothorax, Rev. de la tuberc., 1929, x, 420–423.
18. BERNOU, A.: Contribution à l'étude des injections huileuses massives dans la plèvre, Rev. de la tuberc., 1926, vii, 345–395.
FONTAINE, J.: Résultat de cent oléothorax, Rev. de la tuberc., 1928, ix, 769–774. Oleothorax: indications, technique and results, 1929, G. Doin, Paris.
19. WEIL, P. E., and ISCH-WALL, P.: Treatment of suffocating pneumothorax, Bull. et mém. Soc. méd. d. hôp. d. Par., 1923, xlvii, 127–130.
WEIL, P. E., DARBOIS, E., and POLLET: Spontaneous pneumothorax and oleothorax, Ibid., 1923, xlvii, 1382–1385.
20. BERNOU, A.: L'Oléothorax, Presse méd., 1932, xl, 1139–1141.
21. THIN, E.: L'Oléothorax, 1923, A. Legrand, Paris.
22. UNVERRICHT and DOSQUET: Methode zur Vermeidung von Pneumothorax-exsudaten, Deutsch. med. Wchnschr., 1933, lix, 451–452.
23. HEISE, F. H., and PAINE, D.: Pleural fluids during artificial pneumothorax treatment in pulmonary tuberculosis, Trans. Am. Clin. and Climat. Assoc., 1934, l, 246–257.
24. BAUMGARTEN, W., and RUSK, H. A.: Oleothorax; its use in chronic non-infectious pleural effusion, South. Med. Jr., 1932, xxv, 239–242.
25. DAVIES, W. J.: Use of gomenol in tuberculous empyema, Am. Rev. Tuberc., 1931, xxiv, 263–275.
LABESSE, P., and MARIE, J. C.: De la place que doit tenir l'oléothorax dans la collapsothérapie de la tuberculose pulmonaire, Rev. de la tuberc., 1930, xi, 648–666.
FONTAINE, J.: See reference 18.
MUNRO, N. M.: Oleothorax, with observations on 20 cases, Brit. Med. Jr., 1932, i, 554–558.
DANIELLO, L., and ALEXANDROV, M.: Analyse des resultats obtenus dans 46 cas de tuberculose traités par l'oléothorax, Rev. de la tuberc., 1931, xii, 1171–1178.
CARMICHAEL, D. A.: Oleothorax treatment of purulent tuberculous effusions, Canad. Med. Assoc. Jr., 1932, xxvii, 160–163.
MCMAHON, B. T.: Therapeutic pleural effusions by oleothorax, Am. Rev. Tuberc., 1932, xxvi, 424–426.
HAYES, J. N., and BROWN, L.: Experiences with oleothorax, Jr. Thorac. Surg., 1933, iii, 1–11.
BELCIUGATEANU, L., and POPPER, M.: Sur l'oléotorax thérapeutique, Bull. et mém. Soc. méd. d. hôp. de Bucarest, 1924, vi, 240–243.
26. MATSON, R. W.: See reference 4.

CASE REPORTS

GONORRHEAL SEPTICEMIA AND ERYTHEMA NODOSUM*

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Since the report of two cases of gonococcal septicemia by Hewes [1] in 1894, the publishing of sporadic cases has increased that number to about 150. Only 37 of this number, however, have had as fortunate an outcome as the two cases described by Hewes. We have recently had the opportunity of observing a case of gonococcal septicemia complicated by the presence of erythema nodosum. The fact that this patient was still entirely well when seen 14 months after his discharge from the hospital is, we believe, a source of added interest.

Case Report

A 42 year old colored porter was admitted to the Boston City Hospital on December 30, 1933, complaining of pain in both legs of about two weeks' duration.

Two weeks before admission to the hospital he noticed the onset of symptoms which were suggestive of an acute upper respiratory infection. On the following day he awoke with aching pains in both legs, and became aware of the presence of large, red, painful areas on both legs. He also complained of fever, chills, nausea, frequency and nocturia.

The family and social histories were essentially irrelevant.

The patient was a widower, his wife having died in 1929. There had been no pregnancies, and the cause of her death was unknown to the patient.

His past history was not remarkable as far as childhood diseases were concerned. He had no knowledge of having had chorea or rheumatism, and had had no known contact with tuberculosis. In 1923 a bullet was removed from his left thigh, and in 1930 he was admitted to the Boston City Hospital for four days because of an acute gastritis following an alcoholic debauch.

Symptoms referable to the cardiorespiratory or gastrointestinal systems were not elicited. He gave a history of gonorrheal infection in 1926, but denied lues by name and symptoms. He weighed 148 lbs. on admission to the hospital, and his best weight had been 154 lbs. six months previously.

Physical examination revealed a well developed and well nourished adult negro, lying quietly and comfortably in bed. The skull, scalp and hair were negative. The ears and eyes were normal. The pupils reacted equally and well to light and distance. A slight painless swelling of the right side of the upper lip was noted in addition to the presence of a small scar on the left side of the forehead. The mouth and throat were not remarkable. The neck was negative save for the presence of slight painless adenopathy.

The thorax was symmetrical and expanded equally and well on both sides. The

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apex impulse was plainly visible at the fifth interspace in the midclavicular line. The heart sounds were regular and of good quality. No thrills or murmurs were made out. The aortic second sound was slightly more pronounced than the pulmonic second sound. The lung fields were clear and resonant throughout with no râles. The radial pulses were regular, equal, and synchronous with a rate of 76 per minute. The blood pressure was recorded as 128 mm. of Hg systolic and 76 mm. diastolic.

Examination of the abdomen was negative. No tenderness, masses or spasm were made out. The liver, spleen, kidneys and gall-bladder were not palpable. The genitalia were normal. Rectal examination revealed the presence of a slightly enlarged boggy prostate which was moderately tender on digital palpation. Many pus cells were seen in a smear of the prostatic secretion, but no organisms were noted.

Small, non-tender, firm glands were palpated in both axillae and both posterior cervical chains.

The reflexes and upper extremities were normal. The lower extremities were negative except for the presence of a two-inch scar on the upper and inner aspect of the left thigh, which was the result of an old bullet wound. Two round, red, painful, indurated and symmetrical lesions about two inches in diameter were noted on the anterior surface of both legs midway between the knees and ankles.

The hemoglobin was 80 per cent (Sahli). The leukocyte count, which was 3,600 on admission, rose steadily until January 17, when it reached a peak of 20,500. It then slowly declined, and was 8,500 at the time of discharge from the hospital. The erythrocyte average count was 4,000,000. The differential smear was not remarkable, and no malarial parasites were seen.

Twenty-seven urine specimens showed a variable reaction with a specific gravity ranging from 1.003 to 1.027. Albumin in small amounts was present on four occasions, but sugar was never noted. Microscopic examination of the sediment revealed occasional white cells, rare red cells, and no casts.

The non-protein nitrogen was reported as 42 mg. The Kahn test of his blood was negative. The Widal test was negative. The first blood culture showed a *Staphylococcus albus* contamination. On January 16 the second blood culture was reported as having been positive for *Micrococcus gonorrheae*. The next two cultures on January 19 and 20 showed no growth, but on January 24 a second culture positive for *Micrococcus gonorrheae* was obtained. On January 29 no growth was again reported, but on January 31 a third culture positive for *Micrococcus gonorrheae* was obtained. The eighth blood culture, taken on February 1, was sterile, and on February 6, *Micrococcus gonorrheae* was grown from the blood for the fourth time. The next three blood cultures taken on February 11, March 5, and March 8 showed no growth.

All blood cultures were incubated in blood broth. The four positive cultures showed a moderate degree of hemolysis at the end of 48 hours. When grown on a blood agar plate, these organisms were recognized as raised, gray or colorless, glistening, moderate sized, non-hemolytic colonies. On direct smear, the organisms were found to be gram negative, biscuit-shaped diplococci of irregular size and variable staining. Agglutination reactions gave a positive result with antigonococcus serum in a dilution of 1 : 400; the same organisms agglutinating with antimeningococcus serum in a dilution of 1 : 200. Sugar fermentations on ascitic agar with the addition of hormone broth showed the invariable ability of this organism to form acid with dextrose and no change with maltose. On the basis of these findings the organism was considered to be *Micrococcus gonorrheae*.

On February 9 a skin biopsy taken from one of the nodes on the left leg was cultured in blood broth. This culture, after 144 hours of incubation, showed no growth.

Examination of the spinal fluid revealed no abnormal findings. The stools were negative.

An electrocardiogram taken on January 30 was reported as showing normal sinus rhythm with a rate of 77 per minute. The PR interval was 0.15 second. The QRS interval was 0.08 second. T_1 and T_2 were upright. T_3 was low. Left ventricular predominance was present.

Roentgenoscopic examinations of the abdomen and chest were negative.

The patient received very little treatment other than salicylates by mouth, prostatic massage, and an increased fluid intake. His frequent chills were accompanied by a septic temperature which persisted for eight weeks. His spleen was never palpable nor did he, at any time, develop audible cardiac murmurs.

By February 22, the fever had subsided, and the skin lesions had cleared entirely. He was discharged well on March 14, 1934.

The patient was admitted to the hospital again on April 1935 for the purpose of checking his physical condition. As far as could be determined, he was perfectly well at this time, and the complement fixation reaction, which unfortunately had been omitted during his previous admission, was now negative.

Discussion

With Faure-Beaulieu's [2] review of 34 cases in 1906, Thayer's [3] review of 20 cases at the Johns Hopkins Hospital in 1922, and the more recent surveys by McCants,[4] Newman,[5] and Solomon et al.,[6] it is seen that the question of gonococcal endocarditis has received periodic and thorough attention. McCant noted 100 published cases in the literature up to 1912. Solomon, Hurwitz, Woodall, and Lamb found an additional 48 cases since then. With few exceptions, these cases have all been of fatal issue. Of the total number of cases reported, there are 10 instances in which the patient survived despite the presence of cardiac involvement,[5, 7–15] a mortality rate of approximately 93 per cent.

It is reassuring to consider that the presence of the gonococcus in the blood stream does not always imply so high a mortality rate. Thomas [16] and Irons [8] believe that instances of mild gonococcal sepsis, which ordinarily recover, are considerably more common than is usually recognized. Its infrequent demonstration is ascribed to the difficulty in culturing the organism, the relatively small number of organisms in the blood stream in any given case, the ill-defined clinical picture, and the failure to recognize a metastatic lesion as evidence of a possibly demonstrable septicemia.[8] More recently it has been suggested that an intermittent bacteremia makes the isolation of the gonococcus from the blood stream more difficult.[17, 18]

A review of the literature reveals 27 reported cases of non-fatal gonococcemia without demonstrable endocarditis.[1, 17–19, 20–38] These cases, in addition to our own, exhibit certain features which are worthy of note. Without exception they all represent instances of protracted fever. In several cases the presence of an enlarged spleen and of a suggestive rash obscured the true diagnosis for a time because of the obvious possibility of typhoid fever.[13, 31]

Of the 28 recovered cases, 18 patients (including our own) had skin manifestations. These skin lesions demonstrate with admirable accuracy the skin manifestations of gonorrhea noted by Leon Perrin [39] and Buschke.[40] Eight patients had a maculo-papular rash,[23, 24, 26, 27, 30, 31, 38] and two of these had additional pustular lesions.[24] Three (including our own) had erythema nodosum,[21, 29] and three patients had a pustular eruption.[22, 25, 28] Siegal described a pleomorphic papulo-pustular rash with associated hemorrhagic areas.[37] In the

remaining three cases one patient had a macular rash,[18] another had a purpuric eruption [17] and the third had an urticarial type of skin lesion.[34]

The simultaneous occurrence of gonococcal septicemia and erythema nodosum in our patient led us to a consideration of the presence of the latter condition. Early observers such as Trousseau,[41] and later, Lendon,[42] and others,[43, 44] recognized these skin lesions as a specific infectious disease of unknown etiology. MacKenzie [45] noted that many of his cases of erythema nodosum exhibited characteristics of the rheumatic state. Others observed that erythema nodosum was often associated with tuberculosis,[46, 47, 48] and the presence of acid fast bacilli was actually noted in histological sections of the nodes.[49, 50] These three conflicting points of view in addition to the well supported concept that this disease is due to streptococcal infection [51, 52] still have staunch adherents.

Ernberg [53, 54] looks upon erythema nodosum as an early manifestation of tuberculosis and considers it to be an autogenous tuberculin reaction. Wallgren [55, 56] adheres strongly to the possibility of a tuberculous etiology and has pointed out the occurrence of epidemics of erythema nodosum in tuberculous families. Collis [57, 58] recognizes erythema nodosum as a type of hyperactive response to different bacterial allergens, and believes that in London, at least, it is most commonly due to tuberculous and hemolytic streptococcus endotoxins. Yet, in a not far-removed clinic, Forman and Whitwell,[59] although accepting erythema nodosum as a reaction of bacterial allergy, insist that the evidence is in favor of the tubercle bacillus. Symes,[60, 61, 62] another British observer, recognizes two forms of the disease: an acute specific fever of essentially unknown etiology, and an allergic form of nodular rash which may be associated with rheumatic fever and tuberculosis. In this country, Hess and Berman [63] have demonstrated cases of both the tuberculous and rheumatic variety.

The obvious fact that erythema nodosum has been reported in association with at least 13 other conditions has gone almost wholly unrecognized.

As early as 1887, Bradley [64] noted the occurrence of erythema nodosum as a manifestation of iodism. This was later supported by Perrin [65] in 1892. Subsequently these skin lesions were noted in association with syphilis,[66, 67] smallpox,[68] phlebitis,[69] meningococcal,[70, 71, 72] gonococcal [21, 29] and pneumococcal septicemia,[73] leprosy,[74] septic sore throat,[75, 76, 77] scarlet fever,[78] the post-influenzal state,[79] chronic ulcerative colitis,[80] lympho-granuloma inguinale,[81] ultraviolet rays,[82] and rat-bite fever.[83]

In view of this imposing array of infectious, chemical, and mechanical factors it seems unreasonable to accept, without qualification, any narrow concept of the etiology of erythema nodosum. The evidence in hand seems to agree with the recent views of Goldberg-Curth [84] who recognizes an idiopathic type of erythema nodosum, the pathogenic organism of which is unknown, and a symptomatic type which may develop in the course of a wide variety of infectious diseases, and as a cutaneous reaction to toxic substances.

In a recent publication Elwell [85] gives an excellent review of the various theories regarding the etiology of erythema nodosum. He also presents an interesting case of erythema nodosum in which the recurrence of the skin lesions was associated with axillary lymphadenitis and dental sepsis. It is his view that the syndrome of erythema nodosum expresses a reaction to various bacterial allergens, the most important of which is tuberculosis.

Summary and Conclusions

1. A case of gonococcal septicemia complicated by erythema nodosum-like lesions with eventual recovery of the patient is presented.

2. The literature on gonococcal septicemia is reviewed. A study of the recovered cases reveals an estimated mortality rate of 93 per cent in those cases of septicemia suffering from endocardial damage. The presence or absence of cardiac damage is an important factor in determining the prognosis.

3. Skin manifestations of various types in association with gonococcal septicemia are seen with sufficient frequency to be regarded as an important diagnostic factor. Although the most common type is a maculo-papular lesion, any of the skin manifestations of gonorrhea may occur such as urticaria, hyperemia, purpura, and erythema nodosum.

4. It is probable that the so-called idiopathic type represents a large group of patients with symptomatic erythema nodosum in whom the causative factors have been overlooked. Any patient presenting the symptom complex of erythema nodosum requires careful study and investigation, for the lesions may occur in the course of a wide variety of infectious, chemical, and mechanical processes.

BIBLIOGRAPHY

1. Hewes, H. F.: Two cases of gonorrheal rheumatism with specific bacterial organisms in the blood, Boston Med. and Surg. Jr., 1894, cxxxi, 513–516.
2. Faure-Beaulieu, M.: La septicémie gonococcique [illegible]uvée par la constatation du gonocoque dans le sang circulant, Thèse de Paris, 190[illegible]
3. Thayer, W. S.: On the cardiac complications of gonor[illegible]a, Bull. Johns Hopkins Hosp., 1922, xxxiii, 361–372.
4. McCants, J. M.: Gonococcus infection of heart, wi[illegible] report of 2 fatal cases due to gram negative diplococcus, U. S. Nav. Med. Bull., 1[illegible], xxviii, 603–613.
5. Newman, A. B.: Prognosis in gonococcal endocarditis; review of literature and report of case with spontaneous recovery, Am. Heart Jr., 1933, viii, 821–833.
6. Solomon, P., Hurwitz, D., Woodall, M., and Lamb, M. E.: Diagnosis of gonococcus endocarditis, Arch. Int. Med., 1933, lii, 1–15.
7. Aubertin and Gambillard: Endocardite blennorrhagique guérie par la sérothérapie antigonococcique, Bull. et mém. Soc. méd. d. hôp. de Par., 1924, xlviii, 512–517.
8. Irons, E. E.: Gonococcemia with a report of six cases in which the gonococcus was isolated from the blood during life, Arch. Int. Med., 1909, v, 601–627.
9. Perry, M. W.: Gonorrheal endocarditis with recovery; case report, Am. Jr. Med. Sci., 1930, clxxix, 599–605.
10. Schaeffer, H., and Baron, P.: Gonococcémie à localisations multiples, articulaires, cardiaques meningée et cutanée, suivie de guérison, Paris méd., 1927, ii, 93–96.
11. Silvestrini, R.: Poliartrite, endocardite, setticemia gonococcica, Riv. crit. di clin. med., 1903, iv, 385.
12. Withington, C. F.: A case of malignant endocarditis with recovery, Boston Med. and Surg. Jr., 1904, cli, 99.
13. Dieulafoy, G.: Gonococcic septicemia, Internat. Clin., 1909, iii, 59–70.
14. Marfan, A. B., and Debré, R.: Gonohémie à manifestations viscérales multiples chez une fillette de 10 1/2 ans (essais de traitement par le vaccin de Wright et le sérum antiméningococcique), Bull. et mém. Soc. méd. d. hôp. de Par., 1910, xxix, 712–723.
15. Buquet, S., and Jaureguy, J. M.: Gonococcemia a localizaciones múltiples, An. de Fac. de med., 1927, xii, 755–757.
16. Thomas, J. D.: Gonorrheal septicemia, with marked cardiac involvement, Med. Rec., 1908, lxxiv, 668–670.

17. Wheeler, G. W., and Cornell, N. W.: Gonococcal bacteremia in woman, with apparent cure by surgical intervention, Jr. Am. Med. Assoc., 1930, xciv, 1568–1570.
18. Garlock, J. H.: Gonococcal bacteremia in woman, with cure by surgical intervention, Jr. Am. Med. Assoc., 1931, xcvii, 999–1000.
19. Krause, P.: Zwei Fälle von Gonokokkensepsis mit Nachweis der Gonokokken im Blute bei Lebzeiten der Patienten, Berl. klin. Wchnschr., 1904, xli, 492–494.
20. Ahman, G.: Zur Frage von der gonorrhoischen Allgemeininfection, Arch. f. Dermat. u. Syph., 1897, xxxix, 323–334.
21. Alexandresco-Dersça, C., and Jonesco, D.: Thyroïdite suppurée gonococcique à la suite d'une gonococcémie avec rhumatisme polyarticulaire et érythème noueux gonococcique, Paris méd., 1932, i, 188–189.
22. Cabot case 13501: An obscure general infection, Boston Med. and Surg. Jr., 1927, cxcvii, 1140–1142.
23. Chevrel, F.: Septicémie gonococcique à caractères de fièvre intermittente; traitement par la vaccinothérapie, Progrès méd., 1912, xxviii, 281–283.
24. Friedberg, C. K.: Gonococcemia with recovery, report of 4 cases, Am. Jr. Med. Sci., 1934, clxxxviii, 271–278.
25. Filler, W.: Gonococcemia with recovery, Jr. Am. Med. Assoc., 1933, c, 1149–1150.
26. Jenkins, J. A.: Gonococcal septicemia, Brit. Med. Jr., 1922, i, 641.
27. NanuMuscel, I., Jonnesco, D., Claudian, I., and Brull, A.: Septicémie gonococcique pure, Presse méd., 1933, xli, 194–195.
28. O'Brien, T. J., and Bancker, E. A., Jr.: Gonococcus septicemia; recovery without cardiac complication; report of case, New England Jr. Med., 1928, cxcviii, 184–187.
29. Prochaska, A.: Bakteriologische Untersuchungen bei gonorrhoischen Allgemeininfektionen, Deutsch. Arch. f[illegible]in. Med., 1905, lxxxiii, 184–196.
30. Rubenstone, A. I., and [illegible]ael, S. L.: Gonococcemia with recovery, Jr. Am. Med. Assoc., 1932, xcix, 1684–1[illegible]5.
31. Thayer, W. S.: On gonor[illegible]eal septicemia and endocarditis, Am. Jr. Med. Sci., 1905, cxxx, 751–779.
32. Ware, M. W.: Gonorrheal [illegible]yositis, Am. Jr. Med. Sci., 1901, cxxii, 40–45.
33. Wynn, W. H.: General gonococcal infection, Lancet, 1905, i, 352–355.
34. Serrantes-Laserre, A. E.: Sobre un caso de septicemia gonococica en un enfermo con abceso de prostata, no operado, Rev. de espec., 1930, v, 259–262.
35. Zadoc-Kahn, Ogliastri, and Wauthier: Un cas de gonococcémie grave suivie de guérison, Gaz. de Hôp., 1926, xcix, 1613–1614.
36. Ravaut, P., and Ducourtioux: Traitement du rhumatisme et des septicémies blennorragiques par les injections intraveineuses de sérum antigonococcique, Ann. de dermat. et Syph., 1927, viii, 266–292.
37. Siegal, L. A.: Case of gonococcus septicemia, Bull. Buffalo Gen. Hosp., 1925, iii, 66–69.
38. Bloch, M., and Hébert, P.: Fièvre pseudo-palustre gonococcémique; guérison par autovaccinothérapie, Bull. et mém. Soc. méd. d. hôp. de Paris, 1920, xliv, 277–279.
39. Perrin, L.: Des déterminations cutanées de la blennorrhagie, Ann. de Dermat. et Syph., 1890, i, 773–792.
40. Buschke, A.: Über Exantheme bei Gonorrhoe, Arch. f. Dermat. u Syph., 1899, xlviii, 181.
41. Trousseau, A.: Lectures on clinical medicine, New Sydenham Society Trans., 3rd ed., 1868, Lecture VIII, p. 239.
42. Lendon, A. A.: Nodal fever (febris nodosa); synonyms: erythema nodosum, erythema multiforme, 1905, Ballière, Tindall and Cox, London.
43. Gosse, A. H.: Erythema nodosum; an analysis of 100 cases, Practitioner, 1913, xci, 240–252.
44. Comby, J.: Erythème noueux chez les enfants, Arch. de méd. d. enf., 1923, xxvi, 329–342.
45. MacKenzie, S.: Erythema nodosum, especially dealing with its connection with rheumatism, Brit. Med. Jr., 1886, i, 741.

46. Uffelmann, J.: Über die ominöse Form des Erythema nodosum, Deutsch. Arch. f. klin. Med., 1876, xviii, 313–318.
47. Meara, F. S., and Goodridge, M.: The relationship between erythema nodosum and tuberculosis, with the report of a case, Am. Jr. Med. Sci., 1912, cxliii, 393–397.
48. Bronson, E.: Erythema nodosum associated with tuberculosis, Brit. Jr. Child. Dis., 1918, xv, 91–101.
49. Landouzy, L.: Erythème noueux et septicémies à bacilles de Koch, Presse méd., 1913, xxi, 941.
50. Arena, A.: Existencia del Mycobacterium tuberculosis en el nódulo del eritema nudoso, Rev. Soc. argent. de biol., 1933, ix, 542–547.
51. Rosenow, E. C.: The etiology and experimental production of erythema nodosum, Jr. Infect. Dis., 1915, xvi, 367–384.
52. Slot, G.: Erythema nodosum treated with antistreptococcal serum, Lancet, 1934, ii, 600.
53. Ernberg, H.: Erythema nodosum, Nord. med. tidskr., 1932, iv, 230–236. (*Abstr.*, Jr. Am. Med. Assoc., 1932, xcix, 274.)
54. Ernberg, H.: Erythema nodosum and tuberculosis, Am. Jr. Dis. Child., 1933, xlvi, 1297–1307.
55. Wallgren, A.: Epidemisches Auftreten von Erythema nodosum, Beitr. z. Klin. d. Tuberk., 1922, liii, 143–151.
56. Wallgren, A.: Tubercle bacilli in children with erythema nodosum; demonstration by gastric lavage, Am. Jr. Dis. Child., 1931, xli, 816–822.
57. Collis, W. R. F.: New conception of etiology of erythema nodosum, Quart. Jr. Med., 1932, i, 141–156.
58. Collis, W. R. F.: Erythema nodosum, Brit. Med. Jr., 1933, ii, 1162–1165.
59. Forman, L., and Whitwell, G. P. B.: Preliminary observations on erythema nodosum, Guy's Hosp. Rep., 1934, lxxxiv, 213–229.
60. Symes, J. O.: Erythema nodosum and rheumatism, Lancet, 1907, i, 207–208.
61. Symes, J. O.: The association of erythema nodosum and tuberculosis, Brit. Med. Jr., 1914, i, 909.
62. Symes, J. O.: Significance of erythema nodosum, Brit. Jr. Dermat., 1932, xliv, 181–187.
63. Hess, J. H., and Berman, S. L.: Erythema nodosum in childhood, Med. Clin. N. Am., 1928, xii, 49–66.
64. Bradley, E. N.: L'iodisme, Thèse de Paris, 1887.
65. Perrin, L.: Un cas d'érythème noueux dû à l'iodure de potassium, Marseille méd., 1892, xxix, 567–574.
66. Janson, A.: Über Erythema nodosum bei Lues secondaria, Dermat. Ztschr., 1911, xviii, 1053–1064.
67. Mazzanti, C.: Sindrome di eritema nodoso in una donna con manifestazioni di sifilide recente in atto, Dermosifilografo, 1933, viii, 505–516.
68. Tullis, W. L.: Case of erythema nodosum following smallpox, Lancet, 1927, i, 654.
69. Achard, C., and Rouillard, J.: Erythème noueux compliqué de phlébite des veines superficielles des membres, Bull. et mém. Soc. méd. d. hôp. de Paris, 1922, xlvi, 1113–1115.
70. Morgan, H. J.: Chronic meningococcus septicemia; a report of two cases, Bull. Johns Hopkins Hosp., 1921, xxxii, 245–254.
71. Montgomery, L. C.: Chronic meningococcal septicemia, Can. Med. Assoc. Jr., 1929, xx, 266–272.
72. Master, A. M.: Meningococcemia with endocarditis, Jr. Am. Med. Assoc., 1931, xcvi, 164–166.
73. Sacquépée, E.: Erythème noueux au cours d'une septicémie à pneumocoques, Bull. et mém. Soc. méd. d. hôp. de Paris, 1921, xlv, 1539–1542.
74. Ribeiro de Souza, S.: Sindromo de eritema nodoso num doente portador de mal de Hansen, São Paulo med., 1932, i, 5–8.

75. Stone, W. R.: Erythema nodosum associated with streptococcic faucitis, New York Med. Jr., 1923, cxviii, 673–674.
76. Shepheard, E.: Septic sore throat complicated by erythema nodosum, Brit. Med. Jr., 1926, i, 902.
77. Goldstein, H. I.: Erythema multiforme and erythema nodosum with streptococcic sore throat, Med. Jr. and Rec., 1931, cxxxiv, 266–267.
78. Móritz, D.: Two cases of erythema nodosum with scarlet fever, Orvosi hetil., 1934, lxxviii, 645–646.
79. Boganovitch, V.: Five cases of post-influenzal erythema nodosum, Arch. Dis. Childhood, 1930, v, 56–59.
80. Brooke, P. A.: Erythema nodosum-like lesions in chronic ulcerative colitis; report of case, New England Jr. Med., 1933, ccix, 233–235.
81. Kleeberg, L.: Lymphogranuloma inguinale mit Erythema nodosum und aphthösen Erscheinungen am Genitale, Dermat. Wchnschr., 1930, xci, 1376–1379.
82. Milian, G.: Erythème noueux par rayons ultra-violets, Rev. franç. de dermat. et de vénéreol., 1933, ix, 286.
83. Ripley, H. S., and Van Sant, H. M.: Rat-bite fever acquired from dog, Jr. Am. Med. Assoc., 1934, cii, 1917–1921.
84. Goldberg-Curth, A.: Pathogenesis of erythema nodosum, Monatschr. f. Kinderh., 1935, lxi, 249. (*Abstr.*, Jr. Am. Med. Assoc., 1935, civ, 1678.)
85. Elwell, L. B.: Erythema nodosum and focal infection, Brit. Med. Jr., 1935, i, 974–975.

ENTERIC CYSTS *

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Enteric cysts, sometimes called enterogenous or developmental cysts, are structurally similar to the intestines. Their cavity, containing a mucoid substance, is usually lined by epithelial cells with an underlying layer of lymphoid tissue and smooth muscle. Increasing internal pressure and consequent impairment of blood supply may cause localized atrophy or other structural changes. According to Ewing,[1] their origin is from some bud or pouch along the intestinal tract, and Evans [2] believes them to be related to the more common diverticula of childhood. The usual location in the ileocecal area may be explained by the fact that there is a remnant here of the vitelline duct or yolk sac. When the proximal end of this pouch remains patent, the result is the typical Meckel's diverticulum.

Since the first description of Fraenkel [3] in 1882, Drennen,[4] Haggard,[5] and Bradley and Hoke [6] have brought the total number of reported ileocecal cysts to twenty-eight. Occurrences elsewhere along the intestinal tract have been reported. Slesinger [7] found an ileal cyst eight feet from the ileocecal valve, Aitken [8] another ileal cyst, McLanahan and Stone [9] two cysts in the rectal area, and Jackson and Ewell [10] one in the mesentery of the transverse colon. These structures have been found even in the thorax (Salvin,[11] Poncher and Milles [12]) where they probably arise from mediastinal alimentary tract rests. Hughes-Jones [13] reviews 55 cases.

The majority of cases have been in childhood, although cysts have been reported in both extremes of life. There is no predilection for either sex and

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there is usually no other developmental defect. Many of the reported ileocecal cysts have been small; the larger ones are rarely more than 10 cm. in diameter.

In the local hospital records of over 80,000 patients no enteric cysts have been recorded. In spite of the rarity their clinical importance must be recognized. They may produce confusing symptoms which simulate intussusception, abdominal tumors, cysts of other kinds, appendiceal abscess, and intestinal obstruction. Infantile pyloric stenosis by its projectile vomiting can usually be differentiated from other forms of obstruction. The clinical picture in adults may be vague and misleading. In general, the symptoms are those due to mechanical pressure, such as pain and obstipation. Other symptoms, however, may arise from intracystic infection, or from hemorrhage, or from the weight of a larger mass. In spite of clinical experience, laboratory studies and roentgenography, after the discovery of an abdominal tumor the final diagnosis is frequently deferred until operative exposure, or even until microscopic studies have been made.

Case Report

A 12 year old white boy was first seen in April 1934, complaining of abdominal soreness and swelling of two days' duration. Eighteen months earlier and again two weeks earlier he had fallen, causing abdominal pain for a few hours. Both falls were considered inconsequential. On examination his doctor had found a large protuberance from a tumor in the left upper abdomen. Otherwise, the history was that of a sound, hardy boy.

Examination showed a normal, healthy, afebrile, athletic appearing child, who had walked into the hospital. Nothing of significance was found except a tumor mass in the left hypochondriac and epigastric regions, which extended to the umbilicus. This was smooth and round, tense, slightly tender and immovable.

The blood cell counts were normal. The urine contained a trace of albumin, and a scant number of hyaline casts.

Roentgen-ray report by Dr. T. A. Pitts: "Fluoroscopic examination of the chest is negative. The filled stomach is pressed upward by a palpable mass. The stomach and duodenal cap are negative. The remainder of the duodenum which partially encircles the mass is extremely narrow and assumes an unusual course. The jejunum runs anteriorly and is flattened. The practically empty colon is not outlined. The mass is fixed and the distorted outline of the duodenum makes it typical of a pancreatic tumor, probably a cyst." (Figure 6.)

Glucose tolerance test, with 70 grams of glucose:

Time	Blood Sugar	Urine Sugar
Fasting	100 mg.	0
30 min.	154 mg.	+++
60 min.	156 mg.	++
120 min.	114 mg.	0

The pre-operative clinical diagnosis of probable pancreatic cyst was based on the history of abdominal injury, the location and the apparently rapid development of the tumor, roentgen-ray studies and glucose tolerance test findings.

At the operation, performed by Dr. G. H. Bunch, there was found attached to the upper surface of the transverse mesocolon and situated well under the cardiac end of the stomach, an irregular, large, cystic mass (figure 1), not adherent, pushing the stomach upward and the transverse colon downward into the pelvis. Its size

and position mechanically widened the duodenal curve, but caused no apparent obstruction. The attachment of the mass to the transverse mesocolon was separated and the tumor removed intact (figure 2), without disturbing the relationship of the viscera and without resection of the gut.

FIG. 1. Anterior view of intact cyst. (Inch scale.)

The pathological report by Dr. H. H. Plowden is as follows. Gross description: "The specimen was a cystic tumor weighing 1,563 grams and measuring 20 by 14 by 11 cm. Its outer surface was smooth, glistening, and studded with occasional dense nodules, about 0.5 cm. in diameter. The tumor was quite tense, giving the impression of considerable pressure within.

"When the cyst was opened a great quantity of thick, stringy, tenacious mucus of a pale, bluish color with occasional white streaks was seen. The inner walls conformed in shape to the general outside shape, except that toward the point of mesenteric attachment a number of low ridges terminated in sharp edges as if they had at one time divided the large cyst into a number of smaller ones. This finding suggested an originally loculated cyst." (Figure 3.)

Microscopic description: "Sections made from various parts of the cyst wall show varying structures, apparently depending on the amount of stretching to which the wall has been subjected. The outer surface covering is of flat, pavement-like endothelial cells, which correspond to the peritoneal covering. Beneath this is a layer of thin, loose connective tissue in which are a few small lymphocytes and small

blood vessels. The greatest variation of structure is seen in the type of lining cells and in the amount of smooth muscle present. In some areas the lining epithelium is a single layer of low cuboidal cells; in others there are several layers of columnar cells; in still others there is a layer of tall columnar cells of the mucus-forming type (figure 4). The latter type of cells predominates. In the thinner parts there are

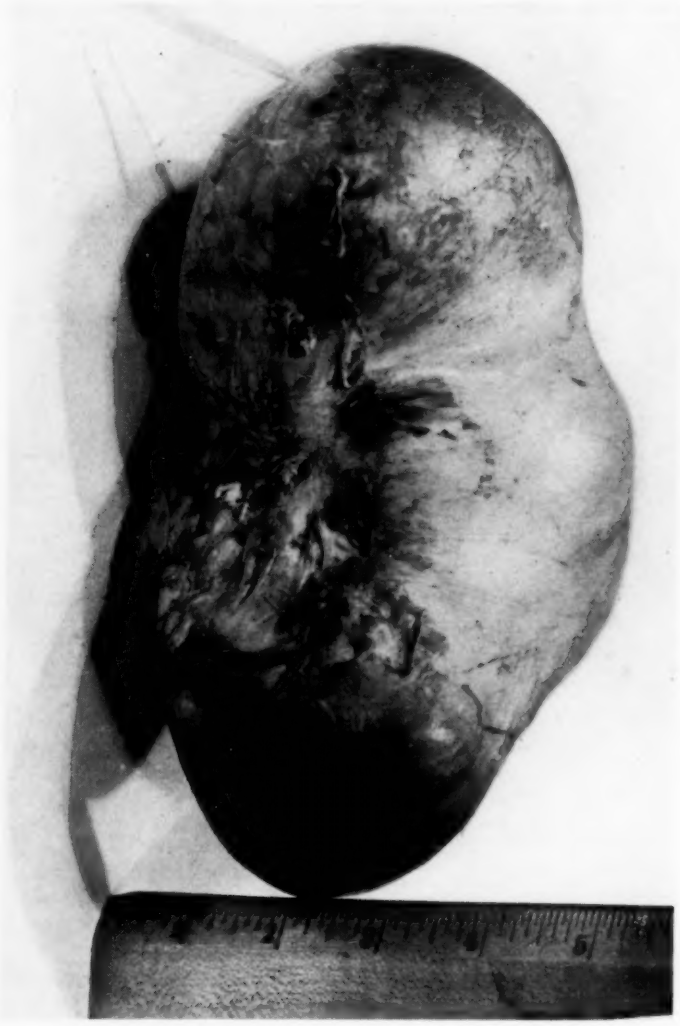

FIG. 2. Showing mesenteric attachment. (Inch scale.)

merely fragments of muscle tissue. In some of the thicker areas there is a well developed muscle layer made up of inner circular fibers and outer longitudinal fibers (figure 5). The histological resemblance to intestine is quite striking. Diagnosis: Enteric cyst."

Convalescence was uneventful and during the 10 months since the operation the boy has been entirely well.

FIG. 3. Interior of cyst. Atrophic ridges suggest a loculated-type tumor.

SUMMARY

Enteric cysts are rare developmental abnormalities which occur anywhere along the alimentary tract although usually in the region of the terminal ileum. Symptoms are usually manifested in early childhood.

This example was found in a 12 year old boy after symptoms of a few days' duration, and the correct diagnosis was made only after microscopic study. The unusual features were (1) its unusual location in the transverse mesocolon, (2) its large size, about one-twenty-fifth of the body weight, and (3) its at-

FIG. 4. Section of cyst wall showing single layer of tall columnar cells, many of a goblet type. (High power.)

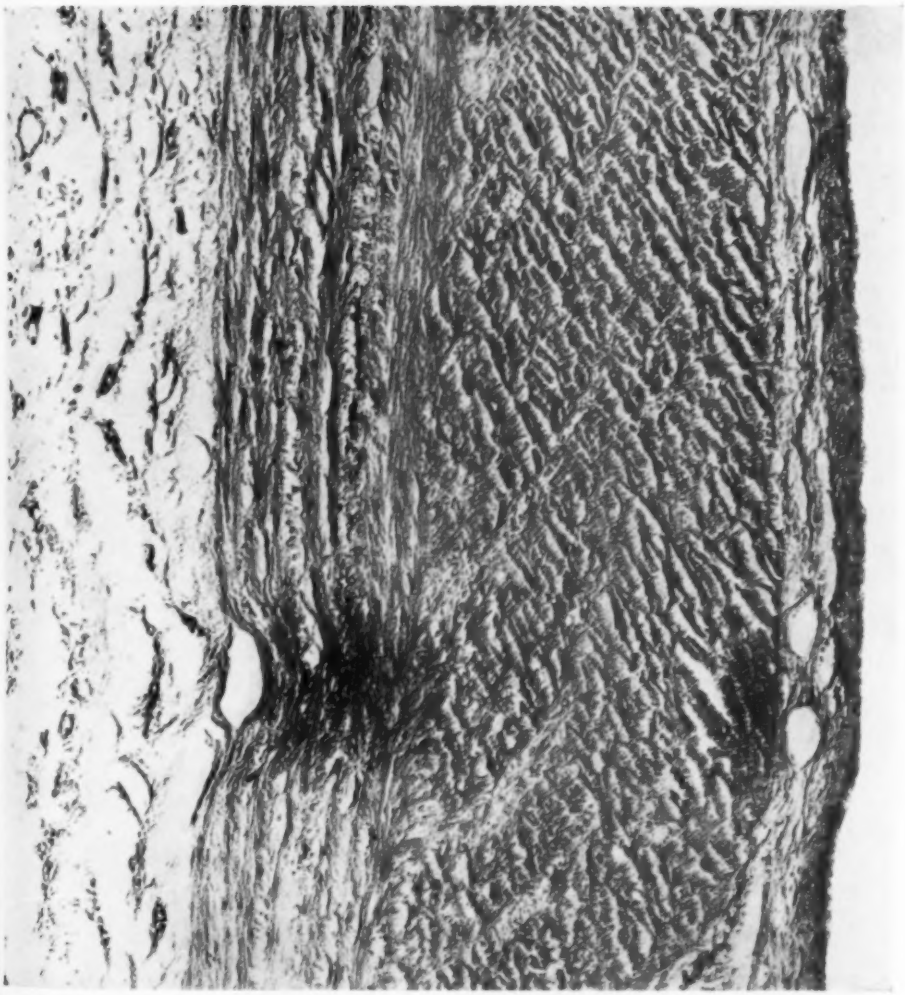

FIG. 5. Section of entire cyst wall showing similarity to intestinal structure. (Low power.)

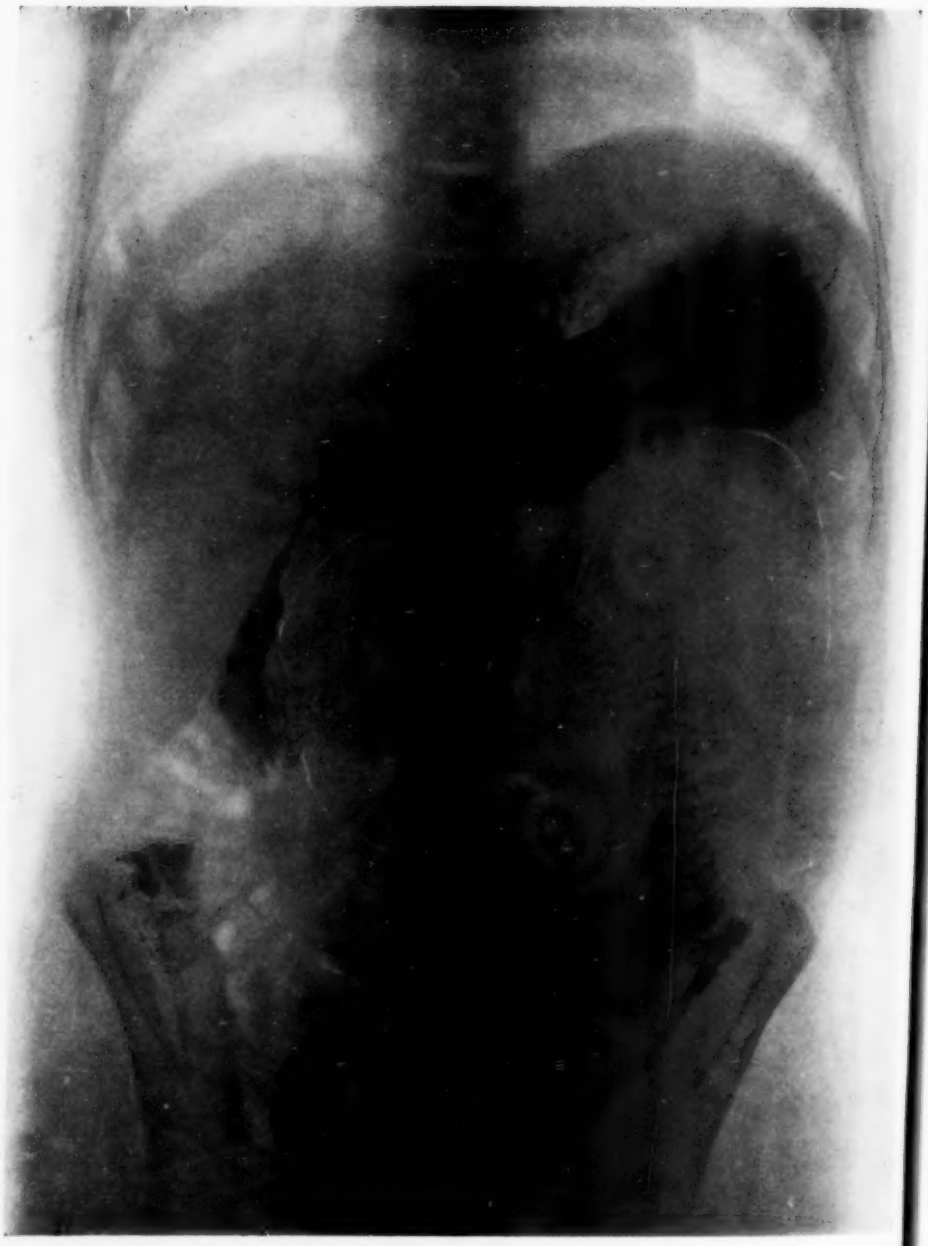

FIG. 6. Retouched film showing site of cyst.

tachment which permitted intact removal without disturbing the adjacent intestine.

BIBLIOGRAPHY

1. Ewing, J.: Neoplastic diseases, 1931, W. B. Saunders, Philadelphia, p. 1030.
2. Evans, A.: Developmental enterogenous cysts and diverticula, Brit. Jr. Surg., 1929, xvii, 34–83.
3. Fraenkel, E.: Über Cysten in Darmkanal, Arch. f. path. Anat., 1882, lxxxvii, 275–285.
4. Drennen, E.: Ileocecal cysts, Arch. Surg., 1931, xxii, 106–120.
5. Haggard, W. D.: Enterogenous cyst of ileum causing obstruction in infants, Surg. Clin. N. Am., 1930, x, 713–717.
6. Bradley, C. E., and Hoke, C. C.: Ileocecal (enterogenous) cyst, Jr. Pediat., 1933, ii, 614–615.
7. Slesinger, E. G.: Enteric cyst of large size in boy, Brit. Jr. Surg., 1928, xvi, 333–334.
8. Aitken, R. Y.: Cyst of ileum, Brit. Jr. Surg., 1931, xviii, 521–523.
9. McLanahan, S., and Stone, H. B.: Enterogenous cysts, Surg., Gynec. and Obst., 1934, lviii, 1027–1029.
10. Jackson, J. A., and Ewell, G. H.: Enteric cysts, Wisconsin Med. Jr., 1929, xxviii, 118–119.
11. Salvin, A. A.: Retroperitoneal cyst, Med. Jr. and Rec., 1928, cxxvii, 256–259.
12. Poncher, H. G., and Milles, G.: Cysts and diverticula of intestinal origin, Am. Jr. Dis. Child., 1933, xlv, 1064–1078.
13. Hughes-Jones, W. E. A.: Enterogenous cysts, Brit. Jr. Surg., 1934, xxii, 134–141.

EDITORIAL

THE MOVEMENT AND DISTRIBUTION OF BODY WATER

It is now fairly well established that sodium and potassium, the two principal basic ions present in the body fluids, have a preponderant influence upon the volume and distribution of body water, as well as upon the regulation of osmotic pressure. Approximately nine-tenths of the total osmotic pressure of the body fluids, under normal conditions, is contributed by the dissolved electrolytes. Proteins, urea and other organic substances usually play a distinctly subordinate rôle. As the contribution of the anions to the total osmotic pressure is about equal to that furnished by the bases, and varies with them, fluctuations in the concentration and excretion of sodium and potassium are of particular significance.

About 70 per cent of the mass of the body is composed of water, which may be separated into two principal divisions from a chemical point of view —the fluid within the cells, and that which bathes the interstitial spaces and comprises the various extracellular fluids, including the blood plasma, lymph and other bodily humors. Owing to the fact that potassium exists in the fluids of the interior of most cells almost to the exclusion of sodium, and that sodium, calculated on the basis of its chemical combining power, or equivalence, accounts for nearly 90 per cent of the bases of the fluids outside of the cells, it is often possible to identify the origin of water discharged from the body by means of the concentrations of these basic electrolytes which are dissolved in it. There is good evidence at the present time, although most of it is indirect, that under ordinary circumstances potassium does not diffuse freely out of the cells and that sodium and chloride do not diffuse into them. The exact amounts of sodium and chloride which are actually present in the intracellular fluids are unknown, but there is reason to believe that at least in many types of cells very little of these electrolytes occur, if indeed they are actually present at all.

In contrast to the relative immobility of the electrolytes, the body water is believed to pass freely in and out of the cell membranes, as required, so as to maintain an equilibrium of the osmotic pressure throughout the body fluids. The pattern of the dissolved substances is fairly constant, but their proper concentrations are stabilized by this shift of water. For the same reason, an excretion of one or both of these ions must necessarily be followed by the excretion of water in order that the concentrations in the body fluids may be maintained at precise level. By studies of the base content of the excreta in disease states, or following the use of diuretic agents, the origin can therefore be surmised. In this manner it has been learned that the dehydration of diabetic acidosis, of severe infantile diarrhea, and following the use of diuretin are all due to a loss of both extracellular and intracellular water. On the other hand, the type present in the condition of heat

cramps, as well as that following the use of thyroxin in myxedema, appears to be due chiefly to a loss of extracellular water.

Fluid, however, does not necessarily follow the movement of electrolytes, or at least it may not move in the same direction. Mackay and Butler have recently reported a disproportionate retention of sodium relative to water during the onset of an acute upper respiratory tract infection, and similar retention of sodium, analogous to the well known retention of chloride, has been reported in pneumonia by Sunderman. Darrow and Yannet, by means of ingenious experiments with intraperitoneal glucose, have removed a large portion of the electrolytes of the extracellular fluids without any gain or loss of water from the body, and have demonstrated the profound dehydration and hemoconcentration which results, due to the passage of water into the cells to equalize the osmotic relationships.

A recently studied type of dehydration and resultant hemoconcentration and shock, that following the withdrawal of the adrenal cortical hormone from adrenalectomized animals, is analogous to the type last mentioned. Here a loss of sodium and chloride in the urine is accompanied by a retention of potassium, and the loss of water by way of the kidney may be almost negligible. In this case, in order to maintain the necessary equality of osmotic pressure both inside and outside of the cellular membranes, water penetrates from the interstitial fluids into the cells, lowering the electrolyte concentration within, while at the same time raising that of the interstitial fluids. The consequence, however, is a hemoconcentration, and the symptoms of dehydration and shock which result are practically identical with those seen when actual losses of fluids occur from the body. The observation is of practical interest, since it illustrates anew, the fact that the clinical phenomena which are observed as a result of hemoconcentration, dehydration, and shock, follow chiefly the loss of extracellular fluids. The intracellular fluid, as in this case, may actually be augmented in amount, but this has no effect upon the dehydration. The body does not lose a significant amount of water, but its displacement into the cells renders it ineffective. The fact that the volume of extracellular fluids, as estimated on theoretical grounds, and as measured by means of the sulphocyanate method introduced by Crandell, or by the sucrose and sulphate distribution studies of Leviates, is not large, as compared to the volume of intracellar fluids, may make more significant the loss of smaller amounts of the former than have hitherto been appreciated. These measurements would indicate that the volume of the interstitial fluids is about 20 to 25 per cent of the body weight, while the fluid within the cells themselves may be twice or even three times as much.

G. A. H.

BOOK REVIEWS

Poliomyelitis; a Handbook for Physicians and Medical Students. By JOHN F. LANDON, M.D., and LAWRENCE W. SMITH. xi + 275 pages; 14.5 × 22.5 cm. Macmillan Company, New York. 1934. Price, $3.00.

This monograph is a very timely addition to the subject of poliomyelitis. It is short and concise and yet is inclusive enough to answer any pertinent question concerning the disease. The opening chapter gives a short historical review of the subject, with especial reference to Heine and Medin, whose names the disease carries. Our present knowledge concerning etiology and pathogenesis is briefly outlined in the second chapter.

The pathology of the disease is especially well covered. This presentation is based on 96 autopsied cases in the Willard Parker Hospital. About 40 pages are devoted to this analysis. The pathology of the reticulo-endothelial system, general systemic pathology, and pathology of the central nervous system are discussed under separate headings. The interesting work of Burrows on the reticulo-endothelial system in poliomyelitis has been more or less corroborated in the authors' series. They agree to "the initial restriction of the infection to the reticulo-endothelial system." The pathological changes in the nervous system are discussed in detail with ample illustrations.

The epidemiology of the disease is fully covered. Such factors as geographic distribution, climate, incidence, effect of season, and the current theories concerning the modes of dissemination are briefly described.

The chapters on symptomatology, paralysis, laboratory aids, and diagnosis are amplified with valuable illustrative cases. The treatment of the disease is discussed at length. All methods currently employed are critically analyzed. The opinion of the authors is that serum therapy is of little or no value in preventing paralysis. The consensus of opinion both for and against serum therapy, however, is discussed. The last chapter gives a valuable short outline on the after care of paralysis, and was written by an orthopedist, Dr. Garry de N. Hough. A short appendix concludes the book. There is an ample bibliography at the end of each chapter, covering 236 titles.

This book can be highly recommended to anyone desiring a concise, authoritative source of information concerning poliomyelitis.

J. G. A., JR.

Recent Advances in Allergy. By GEORGE W. BRAY, M.B., Ch.M., M.R.C.P. xv + 503 pages; 14.5 × 20.5 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1934.

The title "Recent Advances in Allergy" applied to this work to make it uniform with the other members of the "Recent Advances" series, does not express its completeness, as it presents a good general historical review of the study of allergic disease. The author states that his aim is "to provide in a handy and inexpensive form a résumé of our present state of knowledge and the trend of modern research in allergy in general, and its individual manifestations in particular."

The book is divided into two parts, the first discussing the nature of hypersensitiveness, the mechanisms of its manifestations in animals and man, and the general factors involved in allergic diseases. The second division takes up the individual manifestations of allergy: asthma; hayfever; allergic rhinitis; skin diseases; cerebral and gastrointestinal symptoms; bacterial, physical and drug allergies; serum reactions; and hypersensitiveness to animal parasites, fungi, and insects.

The most serious adverse criticism that might be advanced is that the author, in the more practical parts of the book, has written specifically for the English, rather

than the American, practitioner. In such a subject, the geographic distribution of offending plants, with their pollinating periods, is of prime importance, and American flora have been largely neglected. The author states that he has made no effort to present this phase of the subject due to its excellent study in American publications.

In general, "Recent Advances in Allergy" is quite complete, very well documented, and, with the above exception, practical. It should provide a useful and interesting general view of the subject.

T. N. C.

Diseases of the Thyroid Gland. By ARTHUR E. HERTZLER, M.D. 348 pages; 17 × 25 cm. C. V. Mosby Co., St. Louis. 1935. Price, $7.50.

This monograph is described by its author as an expression of his own experiences and impressions in dealing with affections of the thyroid gland. The background is further described as a small country hospital whose isolation makes the investigators more free to follow their own ideas uninfluenced by the opinion of associates. It is, therefore, not intended to be either complete or authoritative, and what is lost in encyclopedic quality is gained in freshness, originality and interest.

There are disadvantages in this approach to the subject. Opinions may be confused with accepted facts, and important recent contributions seem to have limited acceptance by the author. The author, for example, is disinclined to use the classification of the Society for the Study of Goiter, yet much of his discussion elsewhere is argument for this same classification, and his reasons cited for non-acceptance apply nearly as aptly to his own classification.

One may differ with many statements and conclusions, but this difference of opinion is stimulating, and reminds us that many convictions are, after all, only opinions which may be weakened or strengthened by a good argument.

It is to be regretted that one's enjoyment of the book is somewhat marred by occasional lapses from acceptable English.

In spite of certain handicaps the book will be keenly enjoyed by all those interested in diseases of the thyroid gland.

E. M. H., JR.

Objective and Experimental Psychiatry. By D. EWEN CAMERON. 271 pages; 15 × 22 cm. Macmillan Co., New York. 1935. Price, $3.00.

Feeling a "growing distrust of purely descriptive and intuitive concepts of human behavior" and finding it "more and more difficult to content (himself) with facts or assertions save where they will withstand experimentation and will not fail us on prediction," Dr. Cameron points out some of the pitfalls of our usual psychiatric records. He begins by sketching the development of science in general, from a collection of animistic myths to a more or less precise array of formulae buttressed by objectively demonstrable facts, and stresses the need for a study of human behavior from a more detached point of view, affording more demonstrable behavior items in the patient and less injection of the observer's own personality traits. Observational errors, projectionism ("the attempt to ascribe to the patient the feelings and thinking which we consider from our experience he should be entertaining on being exposed to a given situation") and conventionalization (the tendency to make the history of the reaction conform with already delineated concepts) are the greatest defects. This thesis, and possible points of attack for experimental methods, are developed in the first two chapters.

The next 15 chapters survey impartially the literature on: Tests of Intelligence; Introversion—Extraversion; Word Association Tests; Conditional Reflexes; Heredity; Statistics; Blood Sugar Tests; Response to Ephedrin and Adrenalin; Hemoclastic Crisis; Respiratory Center and Schizophrenia; Epilepsy; Basal Metabolism;

Blood Pressure; Sedimentation Rate: Hemo-Encephalic Barrier and pH Relations to Personality; Constitution, and Pathology, in their relation to the problems of abnormal behavior.

The field is thoroughly covered, with references from 300 odd writers on the various subjects. The final chapter is a brief presentation of simple statistical methods. It is a well written book of value to psychiatrists because of the validity of the writer's views and the assembled review of material, and to other physicians who may be interested in current experimentation on the objective aspects of personality.

H. M. M.

Russell A. Hibbs. By GEORGE M. GOODWIN. 136 pages; 15 × 22 cm. Columbia University Press, New York, N. Y. 1935. Price, $2.00.

Everyone who had the good fortune to know Dr. Hibbs will realize how well the author of this treatise has portrayed his character.

Dr. Hibbs was a most striking figure at all times; he spoke with a decisiveness that carried conviction, not only by reason of his deep voice and strong face, but also because he would "back-up" his statements with figures that carried authority. He was keenly interested in developing young surgeons and was always ready to offer counsel, to open pathways for advancement, and to stick by his man; he was a stimulating personality by example as well as by suggestion. Only a very few knew Dr. Hibbs in his lighter moments and it is gratifying to know that he had some real fun from extra-curricular activities, as he was usually seen working hard, early and late.

Some of the original surgical procedures that Dr. Hibbs instituted have become standard throughout the world and have revolutionized the treatment of certain conditions. Thousands of patients are indebted to him for these contributions to surgery as well as to his own personal efforts for them, as individuals.

The New York Orthopedic Hospital with its Country Branch is a lasting monument to Dr. Hibbs and will forever bear witness to his indomitable spirit, wisdom, foresight, perseverance and capability.

The author has written about Dr. Hibbs in a style which flows easily and which gives a clear impression of the striking personality about whom he is writing.

The collection of original papers in the appendix makes the book valuable also as a reference book, and it might well be added to any surgeon's library. The two tributes preceding the appendix express the feelings of the many who have come into intimate contact with this outstanding orthopedic surgeon.

A. F. V.

Synopsis of Regional Anatomy. By T. B. JOHNSTON, M.B., Ch.B., Professor of Anatomy, University of London, Guy's Hospital Medical School. 3rd Edition. Lea and Febiger, Philadelphia. 1935. Price, $4.50.

This book is intended to be used side by side with prepared or recently-dissected specimens, and presupposes a fairly accurate knowledge of each region described. Written in concise but distinctly readable form it gives one the impression of a dissecting manual from which the technical instruction and minute detail have been omitted. Added are occasional practical points which serve to stimulate the student's interest in an otherwise rather abstract study.

Except for that part devoted to the central nervous system it is devoid of illustrations, an acceptable omission in a book of this type, especially as mental pictures are best created from the dissected cadaver itself.

The nomenclature is the English adaptation of the B.N.A., eliminating many of the flaws of the previously-used English terminology and including many new self-

explanatory terms which should with few exceptions find their way into the fuller textbooks. Proper names have been properly excluded.

This book is especially for the student of gross anatomy. It is not a practitioner's book of reference. Put to the purpose for which it is intended it will be a useful adjunct to the student's other books of anatomical instruction.

M. R.

Diseases of the Mouth and Their Treatment. By HERMAN PRINZ, M.D., and SIGMUND S. GREENBAUM, M.D. xiv + 602 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1935. Price, $9.00.

This is a well written and splendidly arranged text dealing with oral disease. The introductory chapters give a comprehensive description of the embryology, anatomy and physiology of the oral cavity. Mouth examination is described, including clinical, roentgenographic and microscopic methods. Oral hygiene and dental prophylaxis are discussed.

Oral manifestations of local origin, as well as those due to metabolic disturbances, blood dyscrasias, avitaminoses, endocrine diseases, infectious diseases, tropical diseases, parasites, skin diseases, drug eruptions, etc. are all well classified, and described in a systematic and thorough manner. Congenital anomalies, and acquired diseases of the tongue, lips, cheek, palate, salivary glands and floor of the mouth receive adequate consideration. There is a comprehensive classification and description of oral tumors and cysts, with methods of diagnosis and treatment.

There is also an interesting discussion of the oral manifestations in functional and organic neurologic conditions: dysarthria, tics, local paralyses, neuralgias, etc.

The closing chapter concerns therapeutic suggestions, such as mouth washes, tooth pastes, ointments and anesthetics.

The book throughout is profusely illustrated with photographs and colored drawings. The method of approach, the completeness of description, and wide range of references make this book authoritative in its field.

B. M. D.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Dr. Clifford J. Barborka (Fellow), Chicago, Ill.—1 book, second edition, "Treatment by Diet";
Dr. Karl E. Kassowitz (Fellow), Milwaukee, Wis.—1 book, "Around A World On Fire";
Dr. David Riesman (Fellow), Philadelphia, Pa., 1 book, "Medicine in the Middle Ages";
New York Homeopathic Medical College, 1 book, "Collected Papers of the New York Homeopathic Medical College and Flower Hospital," containing publications by several members of the College;
Dr. John L. Goforth (Fellow), Dallas, Tex.—1 reprint;
Dr. George C. Griffith (Fellow), Philadelphia, Pa.—1 reprint;
Dr. M. B. Marcellus (Fellow), San Francisco, Calif.—1 reprint;
Lt. Col. S. U. Marietta (Fellow), M.C., U. S. Army—6 reprints;
Dr. Ellen C. Potter (Fellow), Trenton, N. J.—2 reprints;
Dr. William B. Rawls (Fellow), New York, N. Y.—5 reprints;
Dr. Charles F. Tenney (Fellow), New York, N. Y.—1 reprint.

State Meetings of College Members

Connecticut

The first meeting of the Connecticut members of the American College of Physicians was held at the Hartford Hospital, Hartford, Conn., on October 12, 1935. The meeting was held under the chairmanship of Dr. Henry F. Stoll, Governor of the College for the State of Connecticut. Fifty members of the College were in attendance, as were also the College Governors for the New England States, including New Hampshire, Maine, Massachusetts and Rhode Island, and also Dr. James Alex. Miller of New York City, President of the College. A program of clinics was given at the Hartford Hospital, beginning at 11 a.m. and lasting until 4:30 p.m. Dr. James H. Means, Regent of the College from Boston, conducted a clinical pathological conference in the morning, and Dr. A. M. Burgess, Governor for Rhode Island, conducted a similar conference in the afternoon. The social aspects of the meeting included a luncheon through the courtesy of the Avery Convalescent Hospital, a tea through the courtesy of the Neuro-Psychiatric Institute and Hospital and a dinner at the Hartford Club. Dr. O. G. Kiedman was toastmaster at the dinner. Dr. James Alex. Miller, President of the College, delivered an address on College affairs, and Dr. Louis Casamajor of New York City delivered an address on "Interesting Types of Psychoneuroses Met with During the Current Industrial Depression." The meeting as a whole was one of the most successful ones that has been conducted on behalf of the College.

Virginia

During the Virginia State Medical meeting held in Norfolk, October 15 to 17, a dinner was held with 33 Virginia members of the American College of Physicians present at the Monticello Hotel, for the purpose of organizing a more consolidated

unit of the Virginia members of the American College of Physicians. At this meeting Dr. J. Morrison Hutcheson, Governor of the College for Virginia, was elected President and Dr. Frederick C. Rinker of Norfolk was elected Secretary. During the meeting a motion was carried appointing a committee of three, including the President and Secretary, to formulate plans to be presented next autumn at a similar dinner during the state medical meeting.

Members of the Medical Club of Philadelphia and graduates of the University of Pennsylvania recently honored one of the distinguished members of the American College of Physicians, Major General Charles Ransom Reynolds, who has recently been raised to the highest rank, that of the Surgeon General, in the medical service of the U. S. Army. General Reynolds graduated from the University of Pennsylvania School of Medicine in 1899, and has been in the Medical Corps of the U. S. Army for 34 years, being promoted to his present post last June, when he succeeded Major General Robert U. Patterson, who is also a Fellow of this College. General Reynolds will be responsible for the health and welfare of the men of the Army wherever stationed and also for the youths of the CCC who have come under the care of the Army. General Reynolds was born in Elmira, N. Y., in 1877, receiving his medical degree at the age of 22, and interned at "Blockley," the Philadelphia General Hospital. Shortly after entering the Army, he went to the Philippine Islands, where he participated in several battles. After returning to the United States for a short period, he returned to the Philippines again, where he won the Silver Star for gallantry in action in aiding the wounded in a battle on the Island of Jolo. At the opening of the World War he advanced to the rank of Lieutenant Colonel. He went overseas as Division Surgeon of the 77th Division of the American Expeditionary Forces, and participated in the offensives at Aisne-Marne, St. Mihiel and Meuse-Argonne. He was awarded the Distinguished Service Medal for his service in the field and hospitals. Since the war, he was in charge of the School of Instruction at Carlisle Barracks, in Pennsylvania.

General Reynolds' first assistant in the Surgeon General's office is another Fellow of the College, Brigadier General Matthew A. DeLaney, also a graduate of the University of Pennsylvania School of Medicine, Class of 1898. General DeLaney also has a distinguished record in the Army, having served in the Philippine Islands, on the Mexican border and in the World War. He was decorated by the Prince of Wales and cited for gallant and distinguished service by Field Marshal Haig. His entire professional career has been devoted to the Army, except for a few years during the Taft administration when he was the White House physician.

Dr. John N. Simpson (Fellow and Governor of the College for West Virginia), Morgantown, W. Va., has been made Dean Emeritus of the West Virginia University School of Medicine.

Dr. D. O. N. Lindberg (Fellow), medical director and superintendent of the Macon County Tuberculosis Sanatorium, Decatur, Ill., has been reëlected (third term) as Secretary of the Mississippi Valley Sanatorium Association for 1935–36.

The New York Academy of Medicine is conducting its tenth series of Friday afternoon lectures, starting at 4:30 o'clock. The following Fellows are participating:

November 15: Dr. Thomas T. Mackie, Research Associate, Cornell University

Medical College: "The Diagnosis and Treatment of Intestinal Infections Occurring in New York City";

November 22: Dr. Emanuel Libman, Consulting Physician, The Mount Sinai Hospital: "Points in Medical Diagnosis";

December 20: Dr. Ralph Pemberton, Professor of Medicine, Graduate School of Medicine, University of Pennsylvania: "The Present Status of Arthritis and the Treatment of It";

January 3: Dr. Harlow Brooks, Attending Physician, Bellevue Hospital: "Evaluation of Focal Infections from the Internist's Viewpoint";

January 10: Dr. A. S. Blumgarten, Associate Attending Physician, Lenox Hill Hospital: "Recent Advances in Endocrine Research and Their Value in Clinical Practice";

March 6: Dr. Irving S. Wright, Chief of the Vascular Clinic, New York Post-Graduate Hospital: "Diagnosis and Treatment of Peripheral Vascular Disease."

The following Fellows of the College were appointed by the Department of State of the United States as delegates to the International Congress on Gastro-Enterology, held in Brussels, Belgium, during last August:

Dr. Henry L. Bockus, Philadelphia; Dr. Russell S. Boles, Philadelphia; Dr. Max Einhorn, New York; Dr. Sara M. Jordan, Boston; Dr. B. B. Vincent Lyon, Philadelphia; Dr. William Gerry Morgan, Washington, D. C.; and Dr. Franklin W. White, Boston. Among other members of the College who were present at the Congress were Dr. Samuel Weiss (Fellow) and Dr. Anthony Bassler (Fellow), New York; Dr. William A. Swalm (Fellow) and Dr. Harry M. Eberhard (Associate), Philadelphia. The 1937 Congress will be held in Paris.

Dr. David P. Barr (Fellow), St. Louis, was appointed during September to membership on the Council on Pharmacy and Chemistry of the American Medical Association. Dr. A. J. Carlson (Fellow), Dr. G. W. McCoy (Fellow), Dr. A. C. Ivy (Fellow) and Dr. William J. Kerr (Fellow) are members of the Committee for the Protection of Medical Research of the American Medical Association.

Dr. Willard R. Wirth (Associate) has been appointed assistant professor of medicine at the Graduate School of Medicine, Tulane University of Louisiana.

Dr. Dwight O'Hara, professor of preventive medicine, Tufts College Medical School, Boston, has been appointed by Governor Curley of Massachusetts as a member of a public health commission to codify the health laws of the State of Massachusetts, eliminating those which are obsolete and revising others.

The Medical Society of Virginia held its sixty-sixth Annual Session at Norfolk, October 15 to 17, under the presidency of Dr. Francis H. Smith (Fellow), Abingdon. Dr. Arthur C. Christie (Fellow), Washington, D. C., and Dr. James E. Paullin (Fellow and Regent), Atlanta, Ga., were the two guest speakers, whose subjects were "The Answer of the Medical Profession to State Medicine" and "The Significance and Diagnostic Importance of Pain in Disease," respectively. Dr. J. Morrison

Hutcheson (Fellow and Governor for Virginia) was elected President-Elect and Dr. C. Lydon Harrell (Fellow), Norfolk, was elected one of the Vice-Presidents. Dr. Walter B. Martin (Fellow), Norfolk, was elected a delegate to the American Medical Association.

Dr. Hugh S. Cumming (Fellow), Surgeon General of the U. S. Public Health Service, recently gave the dedicatory address of the newly opened isolation pavilion of the Gallinger Municipal Hospital in Washington, D. C.

Dr. Alfred Stengel (Master), Professor of Medicine and Vice-President of the University of Pennsylvania, and Dr. Paul Dudley White (Fellow), Assistant Professor of Medicine at Harvard University Medical School, were the two invited guests on the occasion of the second annual Postgraduate Day of the Medical Institute of the University of Toledo, November 8, on the subject of cardiovascular renal disease.

Dr. George R. Maxwell (Fellow), Morgantown, has been reëlected President of the West Virginia Tuberculosis Association for 1935–36.

Dr. Benjamin H. Orndoff (Fellow), Chicago, is the general secretary for the fifth International Congress of Radiology, to be held in Chicago during September, 1937.

Dr. Bernard T. McGhie (Fellow), Toronto, is acting deputy minister of health of the division of hospitals and the department of health of Ontario.

At the opening exercises of the University of Michigan Medical School at Ann Arbor, Dr. Andrew P. Biddle (Fellow), Detroit, was the recipient of the honorary degree of Master of Arts, "in recognition of a life devoted to the advancement of education and ethics in the medical profession."

Dr. Lowell S. Selling (Associate), Detroit, has been appointed psychiatrist in the recorder's court of Detroit, to succeed Dr. Isaac L. Polozker (Fellow), deceased.

Dr. William J. Stapleton (Fellow), Detroit, has been appointed acting Dean of the Wayne University College of Medicine.

Dr. Joseph F. Bredeck (Fellow), St. Louis, is President of the Missouri Public Health Association.

Dr. Arthur Jackson Patek (Fellow), Milwaukee, founder and for several years editor of the *Wisconsin Medical Journal*, was the recipient of an award for distinguished service by the State Medical Society of Wisconsin at its annual session during

the past autumn. Dr. Patek is a former president of the Medical Society of Milwaukee County and also of the State Medical Society of Wisconsin.

Dr. Charles M. Griffith (Fellow), Washington, D. C., has been elected President of the Association of Military Surgeons of the United States.

Dr. Roscoe L. Sensenich (Fellow), South Bend, has been installed as President of the Indiana State Medical Association for 1936.

Dr. Edwin W. Gehring (Fellow and Governor for Maine) has been named editor of the *Maine Medical Journal.*

Dr. David P. Barr (Fellow), St. Louis, has been chosen as a representative of the St. Louis Medical Society on the newly created Medical-Dental Service Bureau.

A new building for the care of acute cases at the Suffolk Sanatorium, Holtsville, N. Y., has been named for Dr. William H. Ross (Fellow), first president of the county board of health.

Dr. Ralph R. Hendershott (Associate), Tiffin, Ohio, was installed as President of the Ohio State Medical Association at its annual meeting in Cincinnati during October.

Dr. David Riesman (Fellow), Philadelphia, was installed as President of the Inter-State Postgraduate Medical Association at its annual session in Detroit, October 18.

Major Raymond O. Dart (Fellow), Washington, D. C., is acting curator of the Army Medical Museum, succeeding Major Virgil H. Cornell (Fellow).

Dr. Wallace M. Yater (Fellow and Governor for the District of Columbia) is President of the Washington Society of Pathologists.

Dr. C. C. Carpenter (Fellow), professor of pathology at Wake Forest (N. C.) College of Medicine, has been appointed assistant dean of the College.

Dr. Nathaniel B. Heyward (Associate), Columbia, S. C., has been appointed a member of the State Board of Medical Examiners for a four-year term.

OBITUARIES

DR. AUGUST CAILLÉ

Dr. August Caillé (Fellow), New York City, died October 10, 1935, of cerebral hemorrhage at the Lenox Hill Hospital; aged, 81 years.

Dr. Caillé was born in Madison, Indiana; attended the New York College of Pharmacy, graduating in 1873 with highest honors, and then went abroad for the study of medicine at the University of Wurzburg, where he graduated in 1877. Dr. Caillé then returned to America and established himself in the private practice of medicine in New York City, in 1879. He resolved to take an American degree in medicine and enrolled in the College of Physicians and Surgeons of Columbia University, and in 1881 received the degree of medicine from that institution.

Dr. Caillé pursued the study and practice of medicine with much ability and enthusiasm, and was indefatigable in research, especially in the line of children's diseases, on which subject he had become a recognized authority. He was appointed Professor of Medicine and Children's Diseases at the New York Post-Graduate Medical School and Hospital in 1888, an appointment he held for nearly fifty years. At the time of his death, he was Emeritus Professor of Medicine and Pediatrics and Consulting Physician to the Babies' Wards of the New York Post-Graduate Medical School and Hospital, Consulting Physician to the Lenox Hill Hospital, the Sea Cliff Convalescent Home for Babies and Isabella Home. His connections with the Lenox Hill Hospital and the Isabella Home endured for over fifty years.

In the proceedings of many important medical bodies, Dr. Caillé's name appears prominently, for he was elected to many responsible offices. He was an ex-President of the American Pediatric Society, a member of his county medical society, the New York State Medical Society and a Fellow of the American Medical Association, in addition to being an honorary member of the German Medical Society in New York City. In the earliest annals of the American College of Physicians, Dr. Caillé's name appears as a member of its Council. It is further disclosed that he was elected the second Treasurer of the College at the end of 1916, serving for some years thereafter.

Dr. Caillé was deputed as the American delegate to the International Medical Congress in Berlin. He substantially contributed to the medical literature of this country, having published many articles and monographs, the majority of which appeared in leading medical periodicals. He introduced Soxhlet's home sterilization of milk and bottle food for infants to the American profession in 1887. He was one of the first in this country to practice and teach spinal puncture and stomach washing. He gave the first demonstration of O'Dwyer's method of intubation for croup in Germany at Frankfort in 1887. He devised a perforated trocar for abdominal puncture and an automatic tracheal retractor for facilitating tracheotomy for

membranous croup. He suggested permanent drainage for certain forms of dropsy, and devised a scratch test for the detection of individuals sensitized to animal sera.

He was the author of a comprehensive work on "Differential Diagnosis and Treatment of Disease," published in 1906, and also of a presentation of postgraduate teaching entitled, "Prevention and Treatment of Disease."

DR. PEDRO GUTIERREZ IGARAVIDEZ

Dr. Pedro Gutierrez Igaravidez (Fellow), San Juan, Puerto Rico, died May 24, 1935; aged, 64 years.

Dr. Igaravidez was born in San Juan, Puerto Rico, August 24, 1871. He held the degree of Bachelor of Arts from the Instituto Civil, the degree of Bachelor of Science from the Instituto Ensenanaza, Cadiz, Spain, and his medical degree from the University of Sevilla, Spain, 1896. He was formerly Visiting Physician to the Municipal Hospital of San Juan, Medical Director of the Anti-tuberculosis Sanatorium and Member of the Anemia Commission (1904), Chairman of the Puerto Rico Anemia Commission, 1906–10, Director of the Tropical and Transmissible Diseases Service of Puerto Rico, 1910–12, Director of the Institute of Tropical Medicine and Hygiene and Chief of the Laboratory Service of the U. S. Base Hospital in San Juan. He had done postgraduate work at the Polyclinic Hospital of Philadelphia and at the London School of Tropical Medicine in England. He was the author of many published papers.

Dr. Igaravidez was a member of the Royal Society of Tropical Medicine, London; American Society of Tropical Medicine; American Medical Association; American Public Health Association; National Tuberculosis Association; Puerto Rico Medical Association, and had been a Fellow of the American College of Physicians since 1924. He was formerly Clinical Professor of Tropical Medicine in the School of Tropical Medicine of Puerto Rico, conducted under the auspices of Columbia University. At the time of his death, he was Chief of the Division of Roentgenology of the Puerto Rico Department of Health.

Dr. Igaravidez was one of the most prominent clinicians of Puerto Rico and for many years was a close friend and associate of the late Dr. Bailey K. Ashford.

DR. MORGAN SMITH

In the death of Morgan Smith, September 14, 1935, the State of Arkansas lost not only an outstanding leader of the medical profession, but a man who had devoted a large part of his time to the public advancement. Although a general practitioner, Dr. Smith gained his reputation in the field of pediatrics and had done much to further this branch of medicine in the state.

A graduate of the medical departments of the University of Arkansas and Tulane, he began his practice in Little Rock in 1904. Shortly thereafter, Dr. Smith became the state director of the Rockefeller Sanitary Commission for the eradication of hookworm in the South. Out of this commission evolved the Arkansas State Board of Health, and Dr. Smith was its first superintendent.

In 1913, he was appointed Dean of the medical department of the state university and held this position until 1927 when he resigned to resume his private practice. It was under Dr. Smith's régime that the school attained its Grade " A " rating. The pediatric instruction was under his supervision from the time of its introduction in the school until his resignation. He was a member of the American Academy of Pediatrics.

During his lifetime, Dr. Smith had many honors accorded him. He was a past president of the Arkansas Medical Association. He had served on the Council of the Southern Medical Association, and at the time of his death, he was the president of the Arkansas Pediatric Society. He was a Fellow of the College since 1928.

Entering politics in 1929, Dr. Smith was elected to the Arkansas State Senate, and was returned to his seat there for the two following sessions of that body. It was while in the Legislature that he sponsored the Basic Science Law which is now active in medical licensure in Arkansas.

The last two years of his life were spent chiefly at his country home not far from Little Rock. His health had been impaired by cardiac disease, but he was still able to enjoy his many friends and to work among his flowers and vegetables. Death came suddenly as he was enjoying his favorite avocation, reading.

A man of imposing personal appearance, jovial disposition, attractive personality, a peerless raconteur, a skillful and sympathetic physician and a true friend, Morgan Smith made a lasting imprint on the pages of Arkansas medicine.

OLIVER C. MELSON, M.D., F.A.C.P.,
Governor for Arkansas.

DR. HARRY WARDWELL CAREY

Dr. Harry Wardwell Carey (Fellow), Troy, New York, died August 14, 1935, of coronary thrombosis, aged 60 years.

Dr. Carey was born in Stamford, Conn., April 15, 1875. He attended the schools of his native State and was graduated from Yale University with the degree of Bachelor of Arts in 1897 and from Johns Hopkins University School of Medicine with the degree of Doctor of Medicine in 1901. He became assistant bacteriologist and assistant pathologist to the Bender Laboratory for a period of two years. He pursued postgraduate study in dermatology at the University of Munich and at the University of Berlin during 1903, returning to Troy to engage in private practice and to act as

instructor in histology at the Albany Medical College. In 1904 he became instructor in surgical pathology and in 1905 instructor in physical diagnosis. He was pathologist to the Samaritan Hospital from 1904 to 1930; he organized the Society for the Relief of Tuberculosis in 1907; he was bacteriologist for the City of Troy from 1907 to 1926; physician-in-charge of the Lakeview Sanatorium, 1912 to 1916; director of the Social Hygiene Clinic (municipal) from 1919 to 1931; pathologist to the Troy Hospital, 1925 to 1927, and to the Cohoes Hospital from 1927 to 1930. He was attending physician to the Samaritan Hospital from 1930 to the time of his death. As a matter of fact, his death occurred while he was making his rounds at the Samaritan Hospital.

Dr. Carey was a member of the Rensselaer County Medical Society and the New York State Medical Society. He was a Fellow of the American College of Physicians since 1931, and a Fellow of the American Medical Association. He was the author of many published articles and of a book entitled " Bacteriology for Nurses."

Dr. Carey's whole career was marked by an enthusiastic interest in preventive medicine. One of his earliest efforts in Troy was to build up a campaign against tuberculosis. He succeeded in establishing an institution for the treatment of tuberculosis and was named its first supervising physician. As a result of this, the Pawling Sanitarium was later established. It was said that the death rate in Troy from tuberculosis is but a small fraction of that of thirty years ago. Dr. Carey exerted wide influence in other preventive measures such as cancer control, milk inspection, etc. In spite of his varied public activities, he conducted an extensive private practice, until his health compelled him to confine it largely to office and hospital work.

ISAAC LOUIS POLOZKER

Isaac Louis Polozker (Fellow) was born in Grodno, Russia, October 24, 1873. At the early age of five he determined to become a physician, being influenced by four uncles—all members of the medical profession. In 1889 he came to the United States, completed a course at the City College of New York and then moved to Detroit—graduating from the Detroit College of Medicine in 1897. He returned twice to Europe to study, doing postgraduate work in psychiatry at the University of Vienna.

Dr. Polozker was early interested in pediatrics and contributed numerous published articles in that specialty. Later he became interested in psychiatry and became Psychiatrist to the Recorder's Court, Detroit. His long experience in general practice brought to his work in the Psychopathic Clinic a rich equipment of experience, particularly useful in the evaluation of criminality.

Dr. Polozker was a Professor of Clinical Psychiatry at Wayne University and College of Medicine, Detroit; Psychiatrist at the Eloise Hospital

for Mental Diseases; Director of the Psychopathic Clinic of the Recorder's Court; Neuropsychiatrist at St. Mary's Hospital; Member of the Wayne County Medical Society, Detroit Medical Group, Detroit Neurological Society, Michigan State Medical Society; Fellow of the American Medical Association, the American Psychiatric Society, American Teacher's Society and the American College of Physicians.

On August 21, 1935, he passed away suddenly with coronary thrombosis. He is survived by his widow, the former Florence Higer, whom he married in 1919.

J. Frank Kilroy, M.D.

DR. ADOLPH H. NAHMAN

Dr. Adolph H. Nahman (Fellow), San Francisco, Calif., died September 21, 1935; aged 58 years.

Dr. Nahman was born in Poland, and received his preliminary college education at the University of Warsaw. He then entered Northwestern University Medical School, Chicago, from which he received his medical degree in 1909. After graduation, he went to San Francisco, interned at the Southern Pacific Hospital and thereafter became associated with the Mount Zion Hospital, where he attained the position of senior associate of the medical department and chief of the outpatient department. He was a member of the San Francisco County Medical Society, California Medical Association and the American Medical Association, and had been a Fellow of the American College of Physicians since 1926.

Dr. Norman Epstein, in the Bulletin of the San Francisco County Medical Society, has written: "A great doctor has passed. A kindly, pleasant, cheerful soul who knew no hours, no creeds, no caste when the sick called. He gave of his remarkable ability and rich store of knowledge to poor and wealthy alike. . . . Dr. Nahman truly typified the family physician. He entered the homes of his patients as a friend and advisor. He thoroughly knew and understood his people and their peculiarities. He personally supervised and attended upon every technical procedure done upon his patients. . . . As an exponent of the sadly neglected art, bedside medicine, he had no equal. His personal and detailed close observation, combined with comforting and rational therapy based on an alert understanding of every advance in modern medicine, instilled confidence. He spent his life in study and work and attained a perfection in clinical medicine which is rarely reached. . . . Dr. Nahman's interests were not exclusively confined to medicine. His devotion to his family was a prominent feature of his life. He loved music, and his hobbies were photography and gardening. He traveled widely and was much interested in general human affairs. To those who knew him his memory will ever endure."

H. Lisser, M.D., F.A.C.P.,
Governor for northern California.

DR. EMIL JOSEPH SUSSLIN

Dr. Emil Joseph Susslin (Associate), Bridgeport, Conn., died July 9, 1935, of subacute bacterial endocarditis; aged, 37 years.

Dr. Susslin was a graduate of the University of Vermont, 1921. His internship was at the Bridgeport (Conn.) Hospital. At the time of his death, he was Attending Physician to the Englewood Hospital and Assistant Physician at the Bridgeport Hospital. He was a member of the Bridgeport Medical Society, the Fairfield County Medical Society, the Connecticut State Medical Society and the American Medical Association. He became an Associate of the American College of Physicians during 1928.